

(1390 REV. 5-93) US DEPT. OF COMMERCE PATENT & TRADEMARK OFFICE  <div style="text-align: center;"> <b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b> </div>		ATTORNEY'S DOCKET NUMBER 111664  U.S. APPLICATION NO. (if known, sec 37 C.F.R. 1.5)  <div style="text-align: center; font-size: 1.2em;">10/030937</div>
INTERNATIONAL APPLICATION NO. PCT/FR00/02057	INTERNATIONAL FILING DATE July 17, 2000	PRIORITY DATE CLAIMED July 15, 1999
TITLE OF INVENTION USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE		
APPLICANT(S) FOR DO/EO/US Dominique ROECKLIN, Hanno KOLBE, Marie-Hélène CHARLES, Carine MALCUS, Lyse SANTORO, Hervé PERRON		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.		
2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.		
3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).		
4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.		
5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <div style="margin-left: 20px;">           a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).            b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau.            c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US)         </div>		
6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).		
7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <div style="margin-left: 20px;">           a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).            b. <input type="checkbox"/> have been transmitted by the International Bureau.            c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.            d. <input type="checkbox"/> have not been made and will not be made.         </div>		
8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).		
9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).		
10. <input checked="" type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).		
<b>Items 11. to 16. below concern other document(s) or information included:</b>		
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.		
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.		
13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.		
14. <input type="checkbox"/> A substitute specification.		
15. <input type="checkbox"/> Entitlement to small entity status is hereby asserted.		
16. <input type="checkbox"/> Other items or information:		

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) <b>10/030937</b>	INTERNATIONAL APPLICATION NO. PCT/FR00/02057	ATTORNEY'S DOCKET NUMBER 111664
---------------------------------------------------------------------	----------------------------------------------	---------------------------------


17. <input checked="" type="checkbox"/> The following fees are submitted:  <b>Basic National fee (37 CFR 1.492(a)(1)-(5)):</b>  Search Report has been prepared by the EPO or JPO ....\$890.00  International preliminary examination fee paid to USPTO (37 CFR1.482) .....\$710.00  No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....\$740.00  Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....\$1,040.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....\$ 100.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>	<b>CALCULATIONS</b>	<b>PTO USE ONLY</b>																																																																		
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<table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:20%;">Claims</th> <th style="width:20%;">Number Filed</th> <th style="width:10%;">Number Extra</th> <th style="width:20%;">Rate</th> <th style="width:10%;"></th> <th style="width:10%;"></th> </tr> </thead> <tbody> <tr> <td>Total Claims</td> <td>13- 20 =</td> <td>0</td> <td>X \$ 18.00</td> <td>\$</td> <td></td> </tr> <tr> <td>Independent Claims</td> <td>1 - 3 =</td> <td>0</td> <td>X \$ 84.00</td> <td>\$</td> <td></td> </tr> <tr> <td colspan="3">Multiple dependent claim(s)(if applicable)</td> <td>+ \$280.00</td> <td>\$</td> <td></td> </tr> <tr> <td colspan="4"><b>TOTAL OF ABOVE CALCULATIONS =</b></td> <td>\$890.00</td> <td></td> </tr> <tr> <td colspan="4">Reduction by 1/2 for filing by small entity, if applicable.</td> <td>-</td> <td>\$</td> </tr> <tr> <td colspan="4"><b>SUBTOTAL =</b></td> <td>\$890.00</td> <td></td> </tr> <tr> <td colspan="4">Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 month from the earliest claimed priority date (37 CFR 1.492(f)).</td> <td>+</td> <td>\$</td> </tr> <tr> <td colspan="4"><b>TOTAL NATIONAL FEE =</b></td> <td>\$890.00</td> <td></td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">Amount to be refunded</td> <td>\$</td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">Charged</td> <td>\$</td> </tr> </tbody> </table>	Claims	Number Filed	Number Extra	Rate			Total Claims	13- 20 =	0	X \$ 18.00	\$		Independent Claims	1 - 3 =	0	X \$ 84.00	\$		Multiple dependent claim(s)(if applicable)			+ \$280.00	\$		<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$890.00		Reduction by 1/2 for filing by small entity, if applicable.				-	\$	<b>SUBTOTAL =</b>				\$890.00		Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 month from the earliest claimed priority date (37 CFR 1.492(f)).				+	\$	<b>TOTAL NATIONAL FEE =</b>				\$890.00						Amount to be refunded	\$					Charged	\$		
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- a. ☒ Check No. 126891 in the amount of \$890.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 15-0461. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

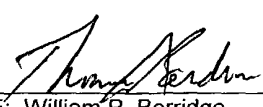
SEND ALL CORRESPONDENCE TO:

OLIFF & BERRIDGE, PLC  
P.O. Box 19928  
Alexandria, Virginia 22320

  
NAME: William P. Berridge  
REGISTRATION NUMBER: 30,024

Date: January 15, 2002

NAME: Thomas J. Pardini  
REGISTRATION NUMBER: 30,411

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) <b>10/030937</b>		INTERNATIONAL APPLICATION NO PCT/FR00/02057		ATTORNEY'S DOCKET NUMBER 111664	
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Reduction by 1/2 for filing by small entity, if applicable.				-	\$
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Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 month from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
<b>TOTAL NATIONAL FEE =</b>				\$890.00	
				Amount to be refunded	\$
				Charged	\$
a. <input checked="" type="checkbox"/> Check No. <u>126891</u> in the amount of <u>\$890.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. <u>15-0461</u> . A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR          1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO: OLIFF & BERRIDGE, PLC P.O. Box 19928 Alexandria, Virginia 22320					
Date: <u>January 15, 2002</u>				 NAME: William P. Berridge REGISTRATION NUMBER: 30,024	
				NAME: Thomas J. Pardini REGISTRATION NUMBER: 30,411	

Res'd PCT/PTO 24 MAY 2002

10/030937

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

BOX: SEQUENCE

Dominique ROECKLIN et al.

Application No.: 10/030,937

Filed: January 15, 2002

Docket No.: 111664

For: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A  
PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE,  
NEUROLOGICAL OR AUTOIMMUNE DISEASE

SUPPLEMENTAL PRELIMINARY AMENDMENT

Director of the U.S. Patent and Trademark Office  
Washington, D.C. 20231

Sir:

In reply to the Notification of Missing Requirements mailed March 27, 2002, please  
amend the above-identified application as follows:

IN THE SPECIFICATION:

At the end of the application, please replace the current Sequence Listing with the  
attached paper and computer-readable Sequence Listing.

REMARKS

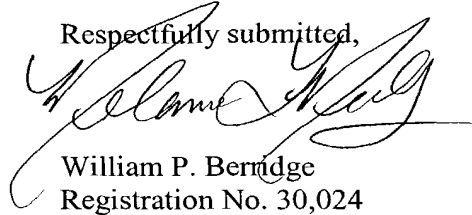
Claims 19-23, 26-30 and 33 are pending.

The attached paper copy and computer-readable copy of the Sequence Listing are  
submitted in compliance with 37 C.F.R. §§1.821-1.825. The contents of the paper copy and  
the computer-readable copy of the Sequence Listing are the same. No new matter is added.  
Support for the information provided in the Sequence Listing can be found in the original  
Sequence Listing.



Early and favorable consideration on the merits is respectfully requested.

Respectfully submitted,



William P. Berridge  
Registration No. 30,024

Melanie L. Mealy  
Registration No. 40,085

WPB:PAC/ja

Attachments:

Sequence Listing (paper and computer-readable copies)

Date: May 24, 2002

**OLIFF & BERRIDGE, PLC**  
**P.O. Box 19928**  
**Alexandria, Virginia 22320**  
**Telephone: (703) 836-6400**

<p>DEPOSIT ACCOUNT USE AUTHORIZATION Please grant any extension necessary for entry; Charge any fee due to our Deposit Account No. 15-0461</p>
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**PATENT APPLICATION**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Dominique ROECKLIN, Hanno KOLBE,  
Marie-Hélène CHARLES, Carine MALCUS,  
Lyse SANTORO, Hervé PERRON

Application No.: US National Stage of PCT/FR00/02057

Filed: January 15, 2002

Docket No.: 111664

For: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A  
PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE,  
NEUROLOGICAL OR AUTOIMMUNE DISEASE

**PRELIMINARY AMENDMENT**

Director of the U.S. Patent and Trademark Office  
Washington, D. C. 20231

Sir:

Prior to initial examination, and after entry of the annexes to the IPER, please amend  
the above-identified application as follows:

**IN THE CLAIMS:**

Please cancel claims 1-18, 24-25, 31-32, and 34-59 without prejudice to or disclaimer  
of the subject matter contained therein.

Please replace claims 22, 23, 26-29 and 33 as follows:

22. (Amended) The polypeptide as claimed in claim 19, characterized in that it comprises  
a protein whose peptide sequence corresponds to SEQ ID No. 9.
23. (Amended) The polypeptide as claimed in claim 19, characterized in that it consists of  
a protein whose peptide sequence corresponds to SEQ ID No. 9.

26. (Amended) A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 19, and then the formation of a complex between said polypeptide and the ligand is detected.
27. (Amended) The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide comprising at least one fragment of a protein chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.
28. (Amended) The method as claimed in claim 26, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. (Amended) A method for detecting at least one polypeptide as defined in claim 19, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
33. (Amended) A nucleotide fragment, characterized in that it encodes a polypeptide as defined in claim 19.

Please add new claims 60-61 as follows:

- 60. The method as claimed in claim 26, characterized in that the biological sample is urine, cerebrospinal fluid or serum.--
- 61. The method as claimed in claim 29, characterized in that the biological sample is urine, cerebrospinal fluid or serum.--

## REMARKS

Claims 19-23, 26-30 and 33 are pending. By this Preliminary Amendment, claims 1-18, 24-25, 31-32 and 34-59 are cancelled and claims 22, 23, 26-29 and 33 are amended to eliminate multiple dependencies and claims 60-61 are added. Prompt and favorable consideration on the merits is respectfully requested.

The attached Appendix includes marked-up copies of each rewritten claim (37 C.F.R. §1.121(c)(1)(ii)).

Respectfully submitted,

Thomas Gordon

William P. Berridge  
Registration No. 30,024

Thomas J. Pardini  
Registration No. 30,411

WPB:TJP/zmc

Attached: APPENDIX

Date: January 15, 2002

**OLIFF & BERRIDGE, PLC**  
**P.O. Box 19928**  
**Alexandria, Virginia 22320**  
**Telephone: (703) 836-6400**

**DEPOSIT ACCOUNT USE  
AUTHORIZATION**  
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necessary for entry;  
Charge any fee due to our  
Deposit Account No. 15-0461

## APPENDIX

## Changes to Claims:

Claims 1-18, 24-25, 31-32, and 34-59 are canceled.

Claims 60-61 are added.

The following are marked-up versions of the amended claims:

22. (Amended) The polypeptide as claimed in claim 19~~one of claims 19 to 21~~, characterized in that it comprises a protein whose peptide sequence corresponds to SEQ ID No. 9.
23. (Amended) The polypeptide as claimed in claim 19~~one of claims 19 to 21~~, characterized in that it consists of a protein whose peptide sequence corresponds to SEQ ID No. 9.
26. (Amended) A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 19~~any one of claims 19 to 23~~, and then the formation of a complex between said polypeptide and the ligand is detected.
27. (Amended) The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide ~~as defined in any one of claims 1 to 5~~ comprising at least one fragment of a protein chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from

Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

28. (Amended) The method as claimed in claim 26 ~~or 27~~, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. (Amended) A method for detecting at least one polypeptide as defined in claim 19 ~~any one of claims 19 to 23~~, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
33. (Amended) A nucleotide fragment, characterized in that it encodes a polypeptide as defined in claim 19 ~~any one of claims 19 to 23~~.

WO 01/05422

18/12

PCT/FR00/02057

**USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING  
OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED  
WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE**

5 The present invention relates in particular to the use  
of at least one polypeptide to obtain a diagnostic,  
prognostic, prophylactic or therapeutic composition for  
for detecting, preventing or treating a pathological  
condition associated with a degenerative and/or  
10 autoimmune and/or neurological disease.

According to the invention, the expression degenerative  
disease is understood to mean a disease in which a  
process of cell death or of cell destruction is  
15 associated with physiological and/or clinical  
disorders. Alzheimer's disease, amyotrophic lateral  
sclerosis and Parkinson's disease are classified  
amongst neurogenerative diseases. The expression  
autoimmune disease is understood to mean a  
20 hyperactivity of the immune system toward one or more  
autoantigens. Multiple sclerosis (MS), rheumatoid  
arthritis (RA) and lupus erythematosus are classified  
among autoimmune diseases.

25 Multiple sclerosis is a chronic disease of the central  
nervous system in humans which progresses through a  
succession of phases of remission and of flare-up or in  
a regular progression and whose anatomicopathological  
characteristic consists in the formation of well  
30 delimited demyelination zones in the white substance of  
the brain and of the spinal cord.

At the histological level, these zones exhibit, at the  
early stage of the lesional process, a degradation of  
35 the periaxonal myelin associated with an impairment of  
the glial cells responsible for this demyelination.  
Inflammatory macrophage activation causing the  
microglial cells (resident tissue macrophages of the

- 2 -

central nervous system), as well as, probably, macrophages from infiltrated blood monocytes, is associated with this demyelination process and contributes to the destruction of the myelinated  
5 sheets. At the center of the demyelinated zone, there is a relative depletion of glial cells whereas a proliferation of astrocytes develops at the periphery and can invade the demyelinated plaque in order to generate a fibrous or gliotic plaque. These sclerotic  
10 structures are responsible for the name given to the disease.

Another characteristic of these plaques is their almost systematic association with a vascular element around  
15 which they develop.

At the histological level, a frequent alteration of the blood-brain barrier (BBB) consisting of capillary endothelium is observed. One of the key elements in  
20 maintaining the BBB consists of the underlying presence of cytoplasmic extensions of the astrocytes, called astrocytic feet. Possibly, the astrocytic feet induce the formation or allow the maintenance of tight joining structures which ensure the cohesion of the capillary  
25 endothelial barrier concretizing the BBB. However, various pathological models report the alteration of the BBB and a depletion of the astrocytic feet.

Moreover, in the lesional process in MS, the alteration  
30 of the BBB contributes toward amplifying the associated inflammatory response by the influx of lymphoid cells from the bloodstream. The contribution of the inflammation associated with the immune cells is important in MS and participates in the lesional  
35 process.

The etiology of MS is the source of a current debate because the disease could have various origins. Hypotheses have been emitted on a bacterial and/or



- 3 -

viral origin. Moreover, as described in patent application WO 95/21859, H. Perron et al. have been led to investigate one or more effector agents for the pathogenic process resulting in the typical formation of demyelination plaques and in astrocytic gliosis. In the context of this study, they demonstrated the presence, in the cerebrospinal fluid (CSF) and the serum of MS patients, of at least one factor which exhibits a toxic activity toward human or animal astrocyte and oligodendrocyte cells. This toxic activity is characterized by a cytomorphological disorganization of the network of intermediate filaments and/or a degradation of the proteins of said filaments and/or a cell death by apoptosis of the glial cells. They established a significant correlation between the *in vitro* detection of this toxic activity in samples of CSF and of serum of MS patients and multiple sclerosis by a quantitative colorimetric assay with methyltetrazolium bromide (MTT) of the live cells, as described in patent application WO 95/21859. Moreover, C. Malcus-Vocanson et al. have shown that urine is a very favorable biological fluid for the detection of the activity of this toxic factor and developed a method using flow cytometry to detect and/or quantify the adherent glial cells which are dead through apoptosis. All the information relating to this method is described in patent application WO 98/11439, whose content is incorporated by way of reference.

Trials were carried out starting with a protein fraction of CSF and of urine from MS patients in order to try to identify this toxic factor. The protein content of each fraction was separated on a 12% SDS-PAGE gel and observed after silver staining of the gel. Among the proteins observed, a protein fraction centered over an apparent molecular weight of about 21 kD was found not predominantly associated with the toxic activity detected *in vitro* and a fraction centered over an apparent molecular weight of about



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precursor of the retinol-binding plasma protein, of the precursor of the ganglioside GM2 activator, of calgranulin and of saposin B. More precisely, the proteins are (i) for the 20 kD band, the C-terminal  
5 fragment of Perlecan which starts at amino acid 3464 and ends at amino acid 3707 (Murdoch AD et al. J Biol Chem, 1992, April 25; 267 (12):8544-47), and designated by a reference in the sequence identifier SEQ ID No. 2 (the full-length Perlecan protein being designated by a  
10 reference in SEQ ID No. 1), (ii) for the 20 kD band, the precursor of the retinol-binding plasma protein (Monaco HL et al., Science, 1995, 268 (5213):1039-1041) whose sequence is given in SEQ ID No. 4 (iii) for the 18 kD band, the precursor of the ganglioside GM2  
15 activator (Furst W et al., Euro J Biochem, 1990, Sep 24; 193(3):709-14) identified in SEQ ID No. 8, (iv) for the 14 kD band, calgranulin B (Lagasse. E et al., Mol Cell Biol, 1988, Jun;8(6):2402-10) identified in SEQ ID No. 17 and (v) for the 8 kD band, saposin B  
20 (Kleinschmidt T et al., Biol Chem Hoppe Seyler, 1988, Dec;369(12):1361-5) represented in SEQ ID No. 24. They have also demonstrated the presence of variant sequences to said reference sequences, in particular for the 18 kD band a variant sequence of the precursor  
25 of the ganglioside GM2 activator designated by the reference SEQ ID No. 9. These variant protein sequences are the product of mutations at the level of the genes encoding said proteins or are the result of splicing phenomena. It should be noted, for example, that  
30 calprotectin is a variant of calgranulin B.

The C-terminal fragment of the Perlecan protein (SEQ ID No. 2) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 69, taking into account the genetic  
35 code. The precursor protein for the retinol-binding plasma protein (SEQ ID No. 4) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 70, taking into account the genetic code. The GM2 activator protein (SEQ ID No. 8) is encoded, for example, by the

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DNA nucleotide sequence SEQ ID No. 31, taking into account the genetic code. The peptides FSWDNCFEGK DPAVIR and YSLPKSEFAV PDLELP derived from the GM2 activator mutated polypeptide (SEQ ID No. 9) are  
5 encoded by the DNA nucleotide sequences SEQ ID No. 66 and SEQ ID No. 67, respectively, taking into account the genetic code. The calgranulin B protein (SEQ ID No. 17) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 42, taking into account the genetic  
10 code. The saposin B protein (SEQ ID No. 24) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 53, taking into account the genetic code.

The expression protein family is understood to mean all  
15 the proteins encoded from the same DNA gene and which result from a differential multiple splicing of the gene and/or of a different reading frame. The DNA gene is transcribed with alternative splicing phenomena, leading to the translation of different primary  
20 sequences of proteins. All these proteins belong to the same protein family. The term "protein family" also includes proteins which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with a reference protein sequence of  
25 the family.

The expression multiple splicing is understood to mean a splicing occurring at least once in the nucleotide region of interest.

30

For example, the expression precursor protein family for the retinol-binding plasma protein designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 4,  
35 SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, and the proteins encoded by the corresponding gene according to different reading frames.

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For example, the expression GM2 activator protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14,, SEQ ID No. 15, SEQ ID No. 16, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame.

For example, the expression calgranulin B protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame. The proteins MRP14 (SEQ ID No. 17) and MRP8 (SEQ ID No. 18) have a different protein sequence while being encoded by the same gene; they belong to the same protein family.

For example, the expression saposin B protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28, SEQ ID No. 29, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame.

The expression nucleic acid family encoding a protein is understood to mean all the cDNA and/or RNA nucleic sequences transcribed from the same DNA gene and which result from a differential multiple splicing. The DNA gene is transcribed with differential splicing



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The expression "splicing" is understood to mean a mechanism of excision of the introns and of joining of the exons during the maturation of the transcripts and the expression "differential splicing" is understood to mean the existence of several schemes for splicing of a primary transcript resulting in the formation of different messenger RNAs and capable of leading to the synthesis of several different proteins (Kaplan and Delpech, Biologie Moléculaire et Médecine, 1993, 2<sup>nd</sup> edition, Médecine et Sciences, Flammarion, pages 73-77). This phenomenon is widely described in the scientific literature. By way of example, there may be mentioned the model of the genes which encode the heavy and light immunoglobulin chains, the model of the gene for dystrophin, the model of the gene for alpha-amylase, the gene for myelin, and the like.

It is known that the eukaryotic genes in particular comprise regions (exons) which encode fragments of the protein encoded by said gene and other regions (introns) which do not have a protein equivalent. This is due to the fact that the genes are first transcribed to a "primary" RNA which is then cut by splicing enzymes at the level of specific nucleotide sites (splicing sites). These enzymes then join the regions encoding the protein, thus reconstituting a "secondary" RNA from which the intron regions have been removed. Moreover, depending on the cellular phenotypes (and therefore the tissues or the differentiation), these enzymes are not all expressed, and thus the same RNA may be differently spliced in the cells of the same individual, thus generating proteins with differences in sequence. However, these phenomena may also be applied to nucleotide regions which are completely coding (exons), but which, according to different possible splicings, will generate several different proteins from the same nucleotide region by the phenomenon of differential splicing between the different protein products.







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of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. In specific embodiments, at least two abovementioned polypeptides are used in combination in order to obtain  
5 a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease.

10 The invention also relates to the use of at least one polypeptide comprising at least one fragment of a protein to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting,  
15 condition associated with a degenerative and/or autoimmune disease, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24 and the peptide  
20 sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the abovementioned peptide sequences. Advantageously, the five polypeptides which correspond to the above definition  
25 are used in combination.

Preferably, the peptide sequence of said polypeptide comprises, or consists of, a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID  
30 No. 17 and SEQ ID No. 24.

The invention also relates to the use of at least one fragment of one of the abovementioned polypeptides for the preparation of an immunogenic peptide, said peptide  
35 comprising all or part of at least one of the sequences designated by the references SEQ ID Nos. 58 to 65 and being used for the production of monoclonal antibodies.

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The subject of the invention is also the use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the above peptide sequences, and the fragments complementary to said fragments, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. It is within the capability of persons skilled in the art to determine the nucleic sequences of the nucleotide fragments from the peptide sequences and the genetic code, this forming part of their general knowledge.

Preferably, said nucleotide fragment encodes a protein which, in the native state, consists of a sequence chosen from any one of the sequences SEQ ID Nos. 1 to 8 and SEQ ID Nos. 10 to 29 cited above, and among the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma

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protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

Another subject of the invention is the use of at least  
5 one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease according  
10 to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID  
15 No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 67, SEQ ID No. 66, SEQ ID  
20 No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.

The invention also relates to the use of a ligand  
specific for a polypeptide or for a nucleotide fragment  
25 as defined above to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease.

30

The expression ligand is understood to mean any molecule capable of combining with a polypeptide, such as a monoclonal antibody, a polyclonal antibody, a receptor, a substrate with enzymatic activity, or an  
35 enzyme for which said polypeptide is a cofactor. The production of polyclonal or monoclonal antibodies forms part of the general knowledge of persons skilled in the art. There may be mentioned, by way of reference, Köhler G. and Milstein C. (1975): Continuous culture of

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fused cells secreting antibody of predefined specificity, Nature 256:495-497 and Galfre G. et al. (1977) Nature, 266:522-550 for the production of monoclonal antibodies and Roda A., Bolelli G.F.:  
 5 Production of high-titer antibody to bile acids, Journal of Steroid Biochemistry, Vol. 13, pp. 449-454 (1980) for the production of polyclonal antibodies.

The expression ligand is also understood to mean any  
 10 molecule capable of combining with a nucleotide fragment, such as a partially or completely complementary nucleotide fragment, a complementary polynucleotide, or an anti-nucleic acid antibody. The production of nucleotide fragments or of  
 15 polynucleotides forms part of the general knowledge of persons skilled in the art. There may be mentioned in particular the use of restriction enzymes, and chemical synthesis on an automated synthesizer, for example on synthesizers marketed by the company Applied Biosystem.  
 20 Moreover, techniques for the production of anti-nucleic acid antibodies are known. There may be mentioned, by way of examples, Philippe Cros et al., Nucleic Acides Researc, 1994, Vol. 22, No. 15, 2951-2957; Anderson, W.F. et al. (1988) Bioessays, 8(2), 69-74; Lee, J.S. et al. (1984) FEBS Lett., 168, 303-306; Malfoy, B. et al. (1982) Biochemistry, 21(22), 5463-5467; Stollar, B.D. et al., J.J. (eds) Methods in Enzymology, Academic Press, pp. 70-85; Traincard, F. et al. (1989) J. Immunol. Meth., 123, 83-91 and Traincard, F. et al.  
 25 (1989) Mol. Cell. Probes, 3, 27-38).  
 30

The subject of the invention is also a method for detecting at least one protein associated with a degenerative and/or autoimmune disease in a biological  
 35 sample in which the biological sample is brought into contact with at least one ligand specific for at least one polypeptide, said polypeptide comprising at least one fragment of a protein and said protein being chosen from the proteins whose peptide sequence in the native

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state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, 5 SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, 10 preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to 29, and the peptide sequences or fragments of said sequences belonging to the same family of proteins. 15 chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B, and then the formation of a complex between said polypeptide and said ligand is detected. Said ligand is advantageously 20 a monoclonal antibody, a polyclonal antibody, a receptor, a substrate with enzymatic activity or an enzyme for which said polypeptide is a cofactor.

Likewise, the invention relates to a method for 25 detecting at least one ligand associated with a degenerative and/or autoimmune disease, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide comprising at least one fragment of a protein, said 30 protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID 35 No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit

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at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID Nos. 10 to SEQ ID No. 29, and the peptide  
5 sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B, and then the formation of a complex  
10 between said polypeptide and said ligand is detected. The ligand is any molecule which satisfies the conditions previously described.

Preferably, in the methods described above, the  
15 sequence of the polypeptide comprises or consists of a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29 above and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan,  
20 the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

The invention also relates to a novel polypeptide which  
25 comprises at least one fragment of a protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment exhibiting at least one mutation, in particular at least two mutations, in relation to the reference sequence SEQ ID No. 8. The polypeptide is  
30 advantageously chosen from the polypeptides which comprise the amino acid sequence FSWDNCFEGKDPAVIR, designated by the reference SEQ ID No. 68, and the amino acid sequence YSLPKSEFAVPDLELP, designated by the reference SEQ ID No. 72.

35

In particular, said polypeptide comprises or consists of SEQ ID No. 9. This polypeptide is used to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing

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or treating a pathological condition associated with a degenerative and/or autoimmune disease, alone or as a mixture with at least one polypeptide as defined above.

5 One of the subjects of the invention is also a nucleotide fragment which encodes the fragment of the protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment of said protein exhibiting at least one mutation, in particular two mutations  
10 relative to the reference sequence SEQ ID No. 8. Said nucleotide fragment in particular comprises or consists of a fragment which encodes SEQ ID No. 9. This fragment is used to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting,  
15 preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease, alone or as a mixture with at least one nucleotide fragment as defined above.

20 The subject of the invention is also a method for detecting at least one ligand associated with a degenerative and/or autoimmune disease, in a biological sample, according to which the biological sample is brought into contact with at least the polypeptide  
25 which comprises or consists of SEQ ID No. 9 or a mixture of polypeptides comprising this polypeptide and at least one polypeptide as described above, and then the formation of a complex or of complexes between the polypeptide(s) and the corresponding ligand(s) is  
30 detected; it is to be understood that the expression ligand is understood to mean a molecule which satisfies the abovementioned conditions.

The invention also relates to a method for detecting at  
35 least the reference polypeptide SEQ ID No. 9 or a fragment of said polypeptide, this fragment comprising at least one and preferably two mutations in relation to the reference sequence SEQ ID No. 8, in a biological sample according to which the biological sample is



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- brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected. The definition of ligand corresponds to that defined above. It may be, inter alia, a monolonal antibody, a polyclonal antibody, a substrate with enzymatic activity or an enzyme for which said polypeptide is a cofactor, or a receptor.
- 10 It is also possible to bring the biological sample into contact with a ligand specific for the reference polypeptide SEQ ID No. 9 and at least one ligand specific for at least one other polypeptide as defined above, and then the formation of complexes between said
- 15 polypeptides and said ligands specific for said polypeptides is detected; it being understood that the expression ligand is understood to mean a molecule which satisfies the conditions described above.
- 20 Another subject of the invention is a nucleotide fragment encoding all or part of the polypeptide SEQ ID No. 9, and its use to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological
- 25 condition associated with a degenerative and/or autoimmune disease, optionally in combination with at least one nucleotide fragment as defined above, and the fragments complementary to said fragments.
- 30 The expression polypeptide fragment is understood to mean at least all or part of the peptide sequence of a protein, in particular a polypeptide fragment which comprises between about 5 and 15 amino acids and more precisely between about 5 and 10 amino acids and 6 and
- 35 15 amino acids. The expression nucleotide fragment is understood to mean at least all or part of a nucleotide sequence, it being understood that the expression nucleotide sequence covers DNA and RNA sequences.

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In particular, the expression polypeptide or nucleotide fragment is understood to mean either fragments associated with the same molecular unit, or fragments in a molecular complex comprising several homologous or  
5 heterologous subunits obtained naturally or artificially, in particular by differential multiple splicing or by selective synthesis.

The invention also relates to a method for detecting at  
10 least one polypeptide as defined above, according to which a sample of a biological fluid is collected from a patient having a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease and, optionally after purification  
15 of said sample of biological fluid, the mass profile obtained from the biological fluid is analyzed by mass spectrometry and compared with a reference mass profile.

20 The present invention also relates to the use of at least one polypeptide of the invention to define therapeutically effective agents, and the use of these agents to prevent and/or treat an autoimmune and/or neurological and/or degenerative disease, and in  
25 particular multiple sclerosis.

Thus, other subjects of the invention are the following:

30 - Use of at least one polypeptide comprising at least one fragment of a protein to test the efficacy of a therapeutic agent, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No.  
35 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID

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No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and  
 5 advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein,  
 10 precursor of the ganglioside GM2 activator, calgranulin B and saposin B;

- Use of at least one polypeptide comprising at least one fragment of a protein to define a biological  
 15 material for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, said protein being chosen from the proteins whose peptide sequence in the native state  
 20 corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No.  
 25 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and  
 30 advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein,  
 35 precursor of the ganglioside GM2 activator, calgranulin and saposin;

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According to an advantageous variant of one of the preceding uses, the polypeptide is chosen from SEQ ID No. 2, 4, 8, 9, 17, 24;

5 - Use of at least one nucleotide fragment to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, according to which said nucleotide fragment is chosen from the  
10 fragments which encode at least one fragment of a protein, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No.  
15 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26,  
20 SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the fragments complementary to said  
25 fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin  
30 B and saposin B.

- Use, to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune  
35 disease, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in the above paragraph;

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- Use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the fragments complementary to said fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B;

- Use, for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in the preceding paragraph.

Advantageously, said nucleotide fragment used encodes said protein.

Preferably, the peptide sequence of said protein in the native state consists of a sequence chosen from any one

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of SEQ ID No. 1 to 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. The polypeptides are preferably chosen from SEQ ID No. 2, 4, 8, 9, 17, 24.

- Use of at least one nucleotide fragment to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, according to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ ID No. 69, SEQ ID No. 70, SEQ ID No. 71, and their complementary sequences.

- Use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, according to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No.

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45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, 5 SEQ ID No 68, SEQ ID No. 69, SEQ ID No. 70, SEQ ID No. 71, and their complementary sequences.

The nucleic sequence is preferably chosen from SEQ ID No. 30, 31, 42, 53.

10

- Use of lycorine for the preparation of a composition for preventing and/or treating a degenerative and/or neurological and/or autoimmune disease.

15

The expression therapeutic efficacy is understood to mean the clinical and biological benefit acquired after administration of a therapeutic agent for the purpose of improving or even curing the disease. This benefit 20 is manifested, inter alia, by a reduction in the clinical and biological signs, and in the pathological effects of the disease after clinical analysis by the doctor and/or biological analyses, such as magnetic resonance imaging, analysis of the oligoclonal bands in 25 the cerebrospinal fluid, analysis of evoked potentials and the test for detection of gliotoxicity called bioassay, whose principle is described in patent application WO 98/11439 cited above. This reduction in the clinical signs and pathological effects should 30 result in a benefit for the patient (Schwartz and Lazar, 1995, Elements de statistique médicale et biologique, eds Flammarion; Lazar and Schwartz, 1995, Eléments de statistique médicale et biologique, eds Flammarion). The disease studied is preferably multiple 35 sclerosis.

The expression composition for prophylactic and/or therapeutic use is understood to mean any composition which comprises an effective therapeutic agent. These

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therapeutic agents are capable (i) of qualitatively and/or quantitatively influencing the biological activity and/or the function of the proteins of interest identified in the present invention, preferably the gliotoxic activity and/or (ii) modulating and/or inhibiting the expression of these proteins and/or (iii) reducing the concentration of these proteins in an extracellular and/or intracellular compartment, and/or substituting a nonpathogenic form for a pathogenic, for example mutated, form of one of these proteins and/or modulating their attachment to at least one of their ligands; said ligand being a molecule which satisfies the criteria described above. Various therapeutic agents are produced based on the conventional approaches widely described in the literature. The various groups of therapeutic agents defined from the proteins of interest identified in this present invention are described below. Their prophylactic and/or therapeutic efficacy or activity is evaluated *in vitro* and/or *in vivo*.

Evaluation of the efficacy of a therapeutic agent *in vitro*: urine samples from healthy individuals and from patients suffering from multiple sclerosis, preferably in the active phase, are tested for their gliotoxic activity *in vitro* based on the bioassay protocol described in patent application WO 98/11439, cited above. The experiment is carried out in parallel by adding or otherwise, to the urine samples tested, the therapeutic agent whose efficacy is to be tested. Assays are carried out at various concentrations of this agent, and after various incubation times with the sample, at a temperature of about 37°C or at room temperature, for each concentration of agent tested, before carrying out the bioassay test. The gliotoxic activity is determined for each crude or purified sample of control and patient's urine in the presence or in the absence of tested therapeutic agent. A prophylactic and/or therapeutic agent for multiple



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sclerosis is an agent which allows a reduction or an inhibition of the gliotoxic activity in a biological fluid from the patients, in particular in the urine. This reduction or inhibition is evaluated relative to  
5 the gliotoxic activity detected in the biological fluid of MS patients in the absence of the test agent which defines the upper limit and relative to the gliotoxic activity detected in the urine of a healthy individual which determines the lower limit (Schwartz and Lazar,  
10 1995, Elements de statistique médicale et biologique, eds Flammarion; Lazar and Schwartz, 1995, Elements de statistique médicale et biologique, eds Flammarion). The therapeutic efficacy of several agents may be evaluated in combination in the same assay.

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Evaluation of the efficacy of a therapeutic agent using an animal model: there are injected into an animal fractions of purified urine and/or at least one polypeptide of the invention and/or at least one  
20 protein obtained by genetic recombination which corresponds to at least one polypeptide of the invention and/or at least one synthetic polypeptide whose amino acid sequence corresponds to the sequence of at least one polypeptide of the invention. The  
25 injections are carried out, at various established concentrations, into mammalian animals such as mice or rats, preferably a Lewis rat according to the protocol described in patent application W097/33466 cited above. Various concentrations of a fraction of crude or  
30 purified urine or of at least one polypeptide and/or one protein, as defined above, are injected into a series of animals by the intradermal, intravenous, intrathecal, intracerebral or intramuscular route, and the like. A negative control is carried out in  
35 parallel. The prophylactic and/or therapeutic agent to be evaluated and then injected at various concentrations and by various routes of administration to a mammalian animal, preferably to a mouse or to a rat. The injections are carried out as a single dose or

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as repeated doses, with various time intervals between each administration. A few hours to a few weeks after the administration, biological samples, preferably of blood, serum, cerebrospinal fluid, or urine, are collected. These samples are subjected to:

(i) a measurement of the gliotoxic activity by the bioassay, and/or

(ii) a measurement of activity of the polypeptides and/or proteins of interest of the invention, alone or in combination, as described at least in: Li et al., 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263:6588-6591; Li et al., 1981 J Biol Chem 256:6234-6240; Li et al., 1976 J Biol Chem 251:1159; Kase et al., 1996, FebsLetters 393: 74-76; Kishimoto et al., 1992, J Lipid Res 33: 1255-1267; O'Brien et al., 1991 Faseb J 5: 301-308; Murthy et al., 1993 J Immunol 151: 6291-6301; Murao et al., 1990 Cell growth Differ 1: 447-454, and/or

(iii) an assay of the polypeptides and/or proteins of interest, alone or in combination, by ELISA (Enzyme Linked-Immunsorbant Assay) and/or Western blotting, using antibodies or antibody fragments capable of binding to at least one of the polypeptides and/or proteins of the invention, or their fragment, and/or

(iv) an assay of antibodies specific for the polypeptides and/or proteins of interest or their fragments, alone or in combination or the assay of at least one ligand capable of binding to the polypeptides and/or proteins of interest or their fragments, and/or

(v) an assay of the "helper" and/or cytotoxic cellular immune response induced against the polypeptides and proteins of interest or their fragments and any immunogenic peptide derived from these polypeptides, proteins and fragments, by carrying out, for example, a test of activation *in vitro* of "helper" T lymphocyte cells specific for the antigen administered; by quantifying the cytotoxic T lymphocytes according to the so-called ELISPOT technique described by Scheibenbogen et al., 1997 Clinical Cancer Research 3:

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221-226. Such a determination is particularly advantageous when it is desired to evaluate the efficacy of a vaccine approach for use in a given patient or for diagnosing and/or prognosticating a potential pathological condition by seeking to demonstrate an immune response naturally developed by the patient against the antigen, the polypeptides, the proteins of interest or the immunogenic fragments derived from these proteins.

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The expression "ligand capable of binding to a protein" is understood to mean any molecule capable of recognizing the protein or a portion of the protein. This may be verified for example *in vitro* by Elisa and/or Western blot tests.

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The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated protein of the GM2 activator (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the family of calgranulin B protein (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the family of the saposin B protein (for example SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

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The animal is then sacrificed and histological sections of various tissues are prepared, preferably brain

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sections. Various studies and observations are carried out in order to detect and/or quantify the characteristic effects of the polypeptides and/or active proteins associated with the gliotoxic fraction, that is to say an apoptosis of the glial cells, and/or the opening of the blood-brain barrier and/or a demyelination. The presence or the expression of the polypeptides and/or proteins of interest identified is also observed and/or quantified in these tissues:

- 10 (i) by conventional immunohistological analyses using ligands for the polypeptides and/or proteins of interest and/or their fragments and/or monoclonal or polyclonal antibodies or fragments of said which bind to the polypeptides and/or proteins of interest, or to  
15 their fragments, and/or
- (ii) by conventional *in situ* hybridization techniques using nucleic acid fragments or oligonucleotides defined from polypeptide and/or protein sequences of interest; and/or
- 20 (iii) by PCR and/or RT-PCR amplification techniques *in situ* using nucleic acid fragments or primers defined from polypeptide and/or protein sequences of interest.

The expression antibodies capable of binding to a polypeptide, to a protein or to their fragments is understood to mean any monoclonal or polyclonal antibody and any fragment of said antibodies capable of recognizing the polypeptide, the protein or their fragments. The capacity of the antibodies to recognize said polypeptides, proteins or their fragments is verified *in vitro*, for example by ELISA and/or Western blotting. An antibody capable of binding to the saposin B protein (SEQ ID No. 24) or to any fragment of this protein is described by Misasi et al. 1998, J. NeuroChem. 71:2313 and Klein et al. 1994, BBRC 200: 1440-1448 or may be produced using conventional methods, for example those designated by references above for the production of monoclonal and polyclonal antibodies, by immunization starting with a natural

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protein, a recombinant protein, a synthetic polypeptide or their fragments. The immunogenic peptides for the production of anti-saposin B monoclonal antibodies are the peptides corresponding to the sequences SEQ ID No. 5 61 and SEQ ID No. 62.

For example, an antibody capable of binding to the GM2 activator protein (SEQ ID No. 8) or to any fragment of this protein is illustrated by Yuziuk et al., 1998 J 10 Biol Chem 273: 66-72 or may be produced using conventional methods known to persons skilled in the art. This antibody may for example be produced after injecting into mice or rabbits the natural protein or any fragment, and/or the recombinant protein or any 15 fragment, and/or peptides defined and synthesized from the protein sequence of the protein. The immunogenic peptides used for the production of anti-GM2 monoclonal antibodies are the reference peptides SEQ ID No. 58, SEQ ID No. 59 and SEQ ID No. 60. An antibody 20 capable of binding to the galgranulin B protein (SEQ ID No. 17) or to any fragment of this protein is described by Saintigny et al., 1992 J Invest Dermatol 99: 639-644 and Goebeler et al. 1994 J Leukoc Biol 55: 259-261, or may be produced using conventional methods. The 25 immunogenic peptides for the production of anti-calgranulin B monoclonal antibodies are the peptides corresponding to the sequences SEQ ID No. 63, SEQ ID No. 64 and SEQ ID No. 65. An antibody capable of binding to the mutated GM2 activator protein (SEQ ID 30 No. 9) or to any fragment of this protein may be produced using the conventional methods defined above.

The expression natural protein and fragment is understood to mean any isolated, completely or 35 partially purified protein obtained from a human or animal sample and any fragment obtained from this protein. For example, the natural protein corresponding to saposin B (SEQ ID No. 24) is obtained according to the technique described by Waring et al. 1998 Mol Genet

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Metab 63: 14-25; the natural protein corresponding to the GM2 activator protein (SEQ ID No. 8) according to the technique described by DeGasperi et al., 1989 Biochem J 260: 777-783, Vogel et al., 1987 Arch Biochem  
5 Biophys 259: 627-638, Mitsuyama, 1983 Hokkaido Igaku Zasshi 58: 502-512; Hirabayashi et al 1983 J Neurochem 40: 168-175, Conzelmann et al., 1979 Hoppe Seylers Z Physiol Chem 360: 1837-1849, Li et al., 1976 J Biol  
10 Chem 251: 1159-1163. The natural protein corresponding to calgranulin B (SEQ ID No. 17) is obtained according to the technique described by Hitomi et al., 1996 J Cell Sci 109: 805-815, Van den Bos et al. 1998 Protein Expr Purif 13: 313-318 and Raftery et al. 1996 Biochem J 316: 285-293.

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The expression recombinant protein or fragment of a recombinant protein refers to any protein or protein fragment produced in a prokaryotic or eukaryotic cell from a nucleotide sequence encoding the protein or its  
20 fragment and transfected into the cell, this protein or its fragment then being purified. In general, any cell derived from a prokaryotic or eukaryotic organism may be used in the context of the present invention, but the cells derived from eukaryotic organisms are  
25 preferred. There may be mentioned, by way of example, CHO cells, COS cells, and Semliki cells. For the purposes of the present invention, said cell may be wild type or mutant. For example, the recombinant protein corresponding to saposin B (SEQ ID No. 24) may  
30 be obtained according to the techniques described by Zaltash et al. 1998 Bebbbs letter 423: 1-4 and Qi et al. 1994 J Biol Chem 269: 16746-16753. Such a recombinant protein is at least available from Kase et al. 1996 Febs Lett 393: 74-76. The recombinant protein  
35 corresponding to the GM2 activator protein (SEQ ID No. 8) may be produced by the techniques described by Yuziuk et al. 1998 J Biol Chem 273: 66-72 and Bierfreund et al., 1999 Neurochem Res 24: 295-300. The recombinant protein corresponding to calgranulin B (SEQ

ID No. 17) may be obtained according to the protocol by Longbottom et al. 1992 Biochim Biophys Acta 1120:215-222, Raftery et al. 1999 Protein Expr Purif 15:228-235. Such a recombinant protein is available at least from  
5 Klempt et al. 1997 Febs Letter 408:81-84.

The expression DNA nucleotide sequence or DNA nucleotide fragment encoding all or part of the saposin B protein (SEQ ID No. 24) is understood to mean the  
10 nucleic acid sequence SEQ ID No. 53 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of the saposin B protein (SEQ ID No. 24) is understood to mean any sequence deduced from the DNA sequence SEQ ID No. 53,  
15 taking into account the genetic code and the splicing phenomena.

The expression DNA nucleotide sequence or DNA nucleotide fragment encoding all or part of the GM2  
20 activator protein (SEQ ID No. 8) is understood to mean the nucleic acid sequence SEQ ID No. 31 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of the GM2 activator protein (SEQ ID No. 8) is understood to mean  
25 any sequence deduced from the DNA sequence SEQ ID No. 31, taking into account the genetic code and the splicing phenomena.

The expression DNA nucleotide sequence or DNA  
30 nucleotide fragment encoding all or part of the calgranulin B protein (SEQ ID No. 17) is understood to mean the nucleic acid sequence SEQ ID No. 42 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of  
35 the calgranulin B protein (SEQ ID No. 17) is understood to mean any sequence deduced from the DNA sequence SEQ ID No. 42, taking into account the genetic code and the splicing phenomena.

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The expression nucleotide sequence or fragment encoding all or part of the mutated protein (SEQ ID No. 9) is understood to mean the nucleic acid sequence deduced from the sequence SEQ ID No. 9, taking into account the genetic code. The expression RNA nucleotide sequence or fragment encoding all or part of this mutated B protein (SEQ ID No. 9) is understood to mean any sequence deduced from the DNA sequence, taking into account the genetic code and the splicing phenomena.

10

The expression protein activity is understood to mean a characteristic biological function of the protein. The protein activity may be demonstrated by techniques known to persons skilled in the art. For example, the activity of saposin B (SEQ ID No. 24) and of the proteins of the saposin B family (for example SEQ ID No. 25 to 29) may be detected using the protocols described by Li et al., 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263: 6588-6591, Li et al., 1981 J Biol Chem 256: 6234-6240 and Li et al., 1976 J Biol Chem 251:1159. The expression activity of the GM2 activator protein (SEQ ID No. 8) and of the proteins of the same family (for example SEQ ID No. 10 to 16) is understood to mean at least the activity detected using the protocols described, for example, by Kase et al., 1996, Febs Letters 393: 74-76, Kishimoto et al., 1992, J Lipid Res 33:1255-1267 and O'Brien et al., 1991 Faseb J 5: 301-308. The expression activity of calgranulin B (SEQ ID No. 17) and the proteins of the same calgranulin B family (for example SEQ ID No. 18 to 23) and any is understood to mean at least the activity detected using the protocols described for example by Murthy et al., 1993 J Immunol 151: 6291-6301 and Murao et al., 1990 Cell growth Differ 1: 447-454.

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Production of a transgenic animal, preferably murine, model for a human pathology can be technically achieved. Briefly, the transgenic animal is produced using the conventional techniques described and



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possesses, integrated into the genome, the nucleic acids encoding the proteins or their fragments.

Evaluation of the efficacy of a therapeutic agent and  
5 therapeutic monitoring *ex vivo*, in humans:

the therapeutic agents to be tested for a therapeutic activity and/or for therapeutic monitoring are administered by various routes to humans, such as the  
10 intradermal, intravenous, intramuscular, intracerebral or oral routes, and the like. Various doses are administered to human beings. The patient's clinical file at the time of the first administration is perfectly known. One or more administrations may be  
15 carried out with various time intervals between each administration which may range from a few days to a few years. Biological samples are collected at defined time intervals after administration of the therapeutic agent, preferably blood, serum, cerebrospinal fluid and  
20 urine. Various analyses are carried out using these samples. Immediately before the first administration of the therapeutic agent, these sample collections and these same analyses are again performed. A conventional clinical and biological examination (MRI, oligoclonal  
25 bands in cerebrospinal fluid, evoked potentials) is also carried out in parallel with the additional analyses which are described below, at various analytical times. The analyses carried out are:

- 30 (i) a measurement of the gliotoxic activity by bioassay starting with samples of serum, CSF and urine, and/or
- (ii) a measurement of the activity of proteins of interest identified in the present invention alone or in combination, as described for example by: Li et al.,  
35 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263: 6588-6591; Li et al., 1981 J Biol Chem 256: 6234-6240; Li et al., 1976 J Biol Chem 251:1159; Kase et al., 1996, FebsLetters 393:74-76; Kishimoto et al., 1992, J Lipid Res 33: 1255-1267; O'Brien et al., 1991

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Faseb J 5: 301-308; Murthy et al., 1993 J Immunol 151: 6291-6301; Murao et al., 1990 Cell growth Differ 1: 447-454; and/or

- (iii) an assay of the proteins of interest or of their  
5 fragments, alone or in combination, in the blood/  
serum, CSF or urine samples by ELISA and/or Western  
blotting, using antibodies or antibody fragments  
capable of binding to at least one of the proteins or  
to one of their fragments, and/or
- 10 (iv) an assay of antibodies specific for the proteins  
of interest or of their fragments in blood/serum, CSF  
or urine samples, by ELISA and/or Western blotting  
using a natural protein or a fragment of the natural  
protein and/or a recombinant protein or a fragment of  
15 this recombinant protein, alone or in combination.  
Likewise, an assay of ligands capable of binding to the  
proteins of interest identified, alone or in  
combination, may be carried out, and/or
- (v) an assay of "helper" and/or cytotoxic cellular  
20 immune response induced against the proteins of  
interest and any immunogenic peptide derived from these  
proteins, for example by carrying out a test of  
activation *in vitro* of T lymphocyte cells specific for  
the antigen administered (example). For example, using  
25 a test of activation *in vitro* of helper T lymphocyte  
cells specific for the antigen administered (example);  
For example by quantifying the cytotoxic T lymphocytes  
according to the so-called ELISPOT technique described  
by Scheibenbogen et al., 1997 Clinical Cancer Research  
30 3: 221-226. Such a determination is particularly  
advantageous when it is desired to evaluate the  
efficacy of a vaccine approach used in a given patient  
or to diagnose a potential pathological condition in a  
patient, seeking to demonstrate an immune response  
35 naturally developed by said patient against the  
antigen, the proteins of interest or any immunogenic  
fragment derived from these proteins, alone or in  
combination, and/or

- (vi) a detection of DNA and/or RNA fragments encoding the proteins or a fragment of proteins of interest by nucleotide hybridization according to techniques well known to persons skilled in the art (Southern blotting, Northern blotting, ELOSA "Enzyme-linked Oligosorbent Assay" (Katz JB et al., Am. J. Vet. Res., 1993 Dec; 54 (12):2021-6 and Francois Mallet et al., Journal of Clinical Microbiology, June 1993, p1444-1449)) and/or by the DNA and/or RNA amplification method, for example by PCR, RT-PCR, using nucleic acid fragments encoding the sequence of the proteins of interest, and/or
- (vii) by tissue, preferably brain, biopsy and observation of the characteristic effects of the active proteins associated with the gliotoxic fraction, that is to say an apoptosis of the glial cells and/or the opening of the blood-brain barrier and/or the observation of demyelination phenomena, and/or
- (viii) by tissue biopsy or on circulating cells (blood, CSF), observation of the presence of proteins of interest and estimation of their expression by immunohistological observation on histological sections prepared from tissues, using ligands and/or antibodies or their fragments capable of binding to the proteins of interest, and/or
- (ix) by tissue biopsy or on circulating cells (blood, CSF), observation of the expression of the proteins of interest by in situ hybridization of the RNA molecules encoding the proteins of interest using nucleic acids defined using the sequences of the proteins of interest, and/or
- (x) by tissue biopsy or on circulating cells (blood, CSF), determination of the expression of the proteins of interest by amplification of these RNAs by conventional techniques such as, for example, RT-PCR, using nucleic acids defined using the sequences of the proteins of interest.

The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal

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fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated GM2 activator protein (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29.

The expression DNA nucleic acid sequence or fragments encoding the "polypeptides and/or proteins of interest of the invention" designates the nucleic acid sequence encoding the C-terminal fragment of Perlecan (SEQ ID No. 2), the nucleic acid sequence encoding the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the nucleic acid sequence (SEQ ID No. 31) encoding the GM2 activator protein (SEQ ID No. 8), the nucleic acid sequence encoding the mutated GM2 activator protein (SEQ ID No. 9), the nucleic acid sequence (SEQ ID No. 42) encoding calgranulin B (SEQ ID No. 17), the nucleic acid sequence (SEQ ID No. 53) encoding saposin B (SEQ ID No. 24), the DNA and RNA nucleic acid sequences (SEQ ID No. 30 to 57) encoding the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins

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or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29).

A protein or a variant of a protein chosen more particularly from the sequences defined in the  
 5 identifiers SEQ ID Nos. 2, 4, 8, 9, 17 and 24 or their fragments, or from the sequences corresponding to the proteins of the families of said sequences (SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 24, SEQ ID No. 25 to 29), and the  
 10 peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination, exhibits a toxic effect directly or indirectly on  
 15 cells, in particular on glial cells, which is demonstrated by the abovementioned bioassay. The autoantibodies produced in response to the presence of this protein or of these proteins are associated with the autoimmune process. Thus, the target of the  
 20 therapeutic agent(s) is for example (i) the natural protein or the natural proteins or their variants with the aim of regulating their expression and/or their intracellular concentration and/or their concentration in the bloodstream, (ii) an antibody specific for at  
 25 least such a protein. The therapeutic agent or the therapeutic agents defined eliminate the target directly, by inducing a specific immune response, and/or neutralize it.

30 The present invention therefore relates to a biological material for the preparation of a pharmaceutical composition for treating mammals suffering from degenerative and/or autoimmune and/or neurological pathological conditions, preferably multiple sclerosis,  
 35 said composition comprising:

(i) either at least one natural protein and/or one recombinant protein or their fragments whose sequence corresponds to all or part of the sequences designated

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by the references SEQ ID No. 2, 4, 8, 9, 17 and 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

(ii) or at least one ligand specific for at least one of said proteins or their fragments whose sequence corresponds to all or part of the sequences designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

(iii) or at least one polyclonal or monoclonal antibody specific for at least one of said proteins or their fragments whose sequence corresponds to all or part of the sequences designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the

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ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit  
5 at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

10 (iv) or at least one nucleic acid sequence comprising at least one gene of therapeutic interest whose nucleic sequence is deduced from the DNA and RNA sequences encoding all or part of the proteins whose sequences are designated by the references SEQ ID No. 2, 4, 8, 9,  
15 17 and 24, and the DNA and/or RNA sequences (for example SEQ ID No. 30 to 57) encoding all or part of the proteins belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the GM2 activator,  
20 calgranulin B and saposin B, in association with elements ensuring the expression of said gene of therapeutic interest *in vivo* in target cells intended to be genetically modified by the nucleic sequence of the gene of therapeutic interest,

25 (v) or at least one mammalian cell not naturally producing the protein of interest or the proteins of interest or any fragment of this or these protein(s) or of the antibodies specific for at least one of said  
30 proteins or of its fragments, said mammalian cell being genetically modified *in vitro* by at least one nucleic acid sequence or a fragment of a nucleic acid sequence or a combination of nucleic acid sequences corresponding to nucleic acid fragments derived from  
35 the same gene or from different genes, said nucleic sequence(s) being deduced from the DNA and RNA sequences encoding the proteins designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the DNA and/or RNA sequences (for example SEQ ID No. 30 to

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- 57) encoding all or part of the proteins belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the GM2 activator, calgranulin B and saposin B, said gene of therapeutic interest encoding all or part of the protein of interest, of a fragment of the protein of interest or of an antibody specific for the protein of interest which will be expressed at the surface of said mammalian cell (Toes et al., 1997, PNAS 94: 14660-14665). The pharmaceutical composition may contain a therapeutic agent alone directed against a target alone or agents taken in combination directed against several targets.
- 15 The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated GM2 activator protein (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.
- 35 From the knowledge of the amino acid sequences of the proteins of interest identified in the present invention, it is within the capability of persons skilled in the art to define and use the molecules described above and/or any molecule capable of binding



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to said molecules, and/or any molecule capable of inhibiting said molecules. Thus, the present invention relates to the use of natural and/or recombinant proteins and/or of synthetic polypeptides and their  
5 fragments, of ligands capable of binding to said proteins or to their fragment(s), for example antibodies; proteins inhibiting the function and/or expression and/or binding of said proteins.

10 Use of natural protein(s) and/or peptide(s) and/or recombinant protein(s) and/or synthetic polypeptide(s) corresponding to the proteins of interest identified in the present invention.

15 The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from an autoimmune disease, preferably multiple sclerosis, comprising:

20 (i) either at least one natural protein and/or one recombinant protein and/or one synthetic polypeptide chosen from the proteins whose amino acid sequences are designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of  
25 said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
30 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, alone or in  
35 combination,

(ii) or at least one natural and/or synthetic fragment of these proteins of interest, for example an

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immunogenic fragment capable of inducing an immune response against a target polypeptide,

(iii) or at least one mimotope peptide defined from the  
 5 reference sequences SEQ ID No. 2, 4, 8, 9, 17 and 24,  
 and the peptide sequences or the fragments of said  
 sequences belonging to the same family of proteins  
 chosen from Perlecan, the precursor of the retinol-  
 binding plasma protein, precursor of the ganglioside  
 10 GM2 activator, calgranulin B and saposin B (for example  
 SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to  
 29), and the peptide sequences which exhibit at least  
 70% identity, preferably at least 80% identity and  
 15 advantageously at least 98 identity with any one of the  
 peptide sequences SEQ ID No. 1 to 29, or a combination  
 of mimotopes, capable of inducing an immune response  
 against the target polypeptide,

(iv) or at least any protein or peptide capable of  
 20 regulating *in vivo* the transcription and/or the  
 translation of the proteins of interest (SEQ ID No. 2,  
 4, 8, 9, 17 and 24) and the peptide sequences or the  
 fragments of said sequences belonging to the same  
 25 family of proteins chosen from Perlecan, the precursor  
 of the retinol-binding plasma protein, precursor of the  
 ganglioside GM2 activator, calgranulin B and saposin B  
 (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
 30 No. 25 to 29) and the peptide sequences which exhibit  
 at least 70% identity, preferably at least 80% identity  
 and advantageously at least 98 identity with any one of  
 the peptide sequences SEQ ID No. 1 to 29. The  
 administration of these proteins and/or peptides alone  
 35 or in combination can reestablish the concentration of  
 a protein of interest in the body.

The immune response directed against a specific antigen  
 may be divided into two distinct categories, one

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involving the antibodies (humoral type immune response), the other the cytotoxic effector cells such as for example the macrophages, the cytotoxic lymphocytes (CTL) or the killer (NK) cells as well as the "helper" T lymphocytes, in particular the CD4+ T lymphocytes (cellular type immune response). More particularly, the two types of response are distinguishable in that the antibodies recognize the antigens under their three-dimensional form whereas the T lymphocytes, for example, recognize peptide portions of said antigens, associated with glycoproteins encoded by the genes of the major histocompatibility complex (MHC), in particular the genes of the type I major histocompatibility complex which are ubiquitously expressed at the surface of the cells or the genes of the type II major histocompatibility complex which are specifically expressed at the surface of the cells involved in the presentation of antigens (APC).

1) According to a first aspect, the cellular type immune response is characterized in that the CD4+ type T cells (helper T cells), following a well-known activation phenomenon (for a review see Alberola 1997, Annu Rev Immunol 15, 125-154), produce cytokines which in turn induce the proliferation of APC cells capable of producing said cytokines, the cellular differentiation of the B lymphocytes capable of producing antibodies specific for the antigen, and the stimulation of the cytotoxic T lymphocytes (CTL).

2) According to a second aspect of the cellular immune response, the cytotoxic effector cells such as for example the CD8+ type lymphocytes (CTL) are activated a) after interaction with antigenic peptides bound to and presented by the glycoproteins carried by the ubiquitous cells and encoded by the genes belonging to the MHC I system, and b) optionally by the cytokines produced by the CD4+ cells.

The present invention relates to the administration of a protein or of a peptide derived from the proteins of

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interest (SEQ ID No. 2, 4, 8, 9, 17 and 24) or of their fragment(s), and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, alone or in combination, for the prophylaxy and/or the therapy of an autoimmune disease, such as multiple sclerosis. These administered proteins and peptides are characterized in that they must have lost their toxic activity, for example their gliotoxic activity, or must have lost their capacity to bind to a ligand, and may significantly induce an immune response mediated by the T lymphocytes and/or the antibodies directed against this protein are used. Such proteins are said to be "modified"; nevertheless, their immunogenicity is preserved. Such modified immunogenic molecules are obtained by a number of conventional treatments, for example chemical or heat denaturation, truncation or mutation with deletion, insertion or location of amino acids. An example of truncation consists in the truncation of amino acids at the carboxy-terminal end which may be up to 5-30 amino acids. The modified molecules may be obtained by synthetic and/or recombinant techniques or by chemical or physical treatments of the natural molecules.

The natural and/or recombinant proteins of interest identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17 and 25), and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the

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ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit  
5 at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s), are used in prophylactic and therapeutic vaccination against autoimmune diseases, preferably MS.

10 A vaccine comprises an immunogenically effective quantity of the immunogenic protein in association with a pharmaceutically acceptable vehicle and optionally an adjuvant and/or a diluent. The pharmaceutically acceptable vehicles, adjuvants and diluents are well  
15 known to persons skilled in the art. There may be mentioned, by way of references, Remington's Pharmaceutical Sciences. The use of vaccine compositions is particularly advantageous in association with an early diagnosis of the disease. The  
20 immunogenic protein is used in the preparation of a medicament for prophylactic or therapeutic vaccination. The proteins of interest may be eliminated from the body without inducing undesirable side effects. The identification of such vaccine proteins or peptides is  
25 carried out as follows: the candidate molecules modified as described above (proteins which are natural or recombinant, peptides) are analyzed in a functional test to verify that they have lost their toxicity, for example their gliotoxic activity, using the test known  
30 as bioassay, and to verify their immunogenicity (i) by carrying out an *in vitro* test of proliferation of CD4+ T lymphocytes specific for the antigen administered (T cell assay) or an *in vitro* test of cytotoxicity of the CD8+ lymphocytes specific for the antigen administered  
35 and (ii) by measuring, *inter alia*, the amount of circulating antibodies directed against the natural protein. These modified forms are used to immunize humans by standard procedures with appropriate adjuvants.

The prepared vaccines are injectable, that is to say in liquid solution or in suspension. Optionally, the preparation may also be emulsified. The antigenic  
5 molecule may be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Examples of favorable excipients are water, saline solution, dextrose, glycerol, ethanol or equivalents and their combinations. If desired, the  
10 vaccine may contain minor quantities of auxiliary substances such as "wetting" or emulsifying agents, pH buffering agents or adjuvants such as aluminum hydroxide, muramyl dipeptide or variations thereof. In the case of peptides, their coupling to a larger  
15 molecule (KLH, tetanus toxin) sometimes increases the immunogenicity. The vaccines are conventionally administered by injection, for example by subcutaneous or intramuscular injection. Additional formulations favorable with other modes of administration include  
20 suppositories and sometimes oral formulations.

In general, the concentration of the polynucleotide in the composition used for administration *in vivo* is from 0.1 µg/ml up to 20 mg/ml. The polynucleotide may be  
25 homologous or heterologous for the target cell into which it will be introduced.

The present invention also relates to the use of vaccines including molecules of nucleic acids which  
30 encode the proteins of interest or immunogenic peptides or their fragment(s), which are non-active, corresponding to the proteins of interest (SEQ ID No. 2, 4, 8, 9, 17 and 24) and the peptide sequences or the fragments of said sequences belonging to the same  
35 family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID

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No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. The  
5 nucleic acid vaccines, in particular the DNA vaccines, are generally administered in association with a pharmaceutically acceptable vehicle by intramuscular injection.

10 From the amino acid sequence of the proteins of interest described (SEQ ID No. 2, 4, 8, 9, 17 and 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-  
15 binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70%  
20 identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, peptides or fragments corresponding to all or part of the primary sequence of these proteins may be synthesized by  
25 conventional methods of peptide synthesis or obtained by genetic recombination.

Recombinant proteins corresponding to the proteins of interest, produced in a prokaryotic or eukaryotic  
30 cellular system, are available from various teams and are described in the literature. They may also be produced by persons skilled in the art from the knowledge of the sequences of the corresponding genes described in the literature and taking into account the  
35 degeneracy of the genetic code. All the protein sequences identified in the present invention are thus capable of being obtained by genetic recombination. The genes are cloned into suitable vectors. Different vectors are used to transform prokaryotic cells (for

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example *E. coli*) and eukaryotic cells (for example COS cells, CHO cells and Simliki cells). The recombinant proteins corresponding to the proteins of interest or to fragments of the proteins of interest may thus be  
5 produced in prokaryotic and/or eukaryotic cellular systems. In *E. coli* cells, the recombinant proteins are produced with a polyhistidine tail. The insoluble protein fraction is solubilized in 8M urea. Enrichment of the product was carried out on nickel-chelated resin  
10 (Qiagen). The column was washed with decreasing concentrations of urea. The elution was carried out with imidazole in the absence of urea. The complete sequence of the proteins of interest may also be cloned into a suitable plasmid and then transferred into the  
15 vaccinia virus in order to obtain a recombinant virus.

Use of ligands capable of binding to the proteins of interest identified in the present invention.

20 The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from an autoimmune disease, preferably multiple sclerosis, comprising:

25 (i) either at least one ligand capable of binding to the proteins and/or fragments of the proteins chosen from the target proteins SEQ ID No. 2, 4, 8, 9, 14 and 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins  
30 chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)  
35 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the ligand



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being capable or not of inhibiting the protein activity,

(ii) or at least one polyclonal or monoclonal antibody  
5 capable of binding to at least one protein or one of  
its fragments chosen from the target proteins SEQ ID  
No. 2, 4, 8, 9, 14 and 24 and the peptide sequences or  
the fragments of said sequences belonging to the same  
10 family of proteins chosen from Perlecan, the precursor  
of the retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
15 No. 25 to 29) and the peptide sequences which exhibit  
at least 70% identity, preferably at least 80% identity  
and advantageously at least 98% identity with any one  
of the peptide sequences SEQ ID No. 1 to 29. This  
antibody may be neutralizing or not, that is to say  
20 capable or not of inhibiting the activity of the  
protein of interest. The ligand may be chosen from any  
molecule or molecule fragment capable of binding to the  
target proteins, for example the receptor for this  
proteins, the cofactors for these proteins, the  
polyclonal or monoclonal antibodies capable of binding  
25 to the proteins or any fragment of these proteins.

These antibodies are very useful in particular for  
allowing the use of therapeutic compositions because  
they lead, for example, to immune reactions directed  
30 specifically against immunodominant epitopes or against  
antigens exhibiting high variability. There are  
administered to the patient either neutralizing soluble  
antibodies in order to inhibit their function, or  
specific soluble antibodies in order to eliminate the  
35 peptide by formation of immune complexes. The invention  
describes the use of antibodies capable of specifically  
recognizing at least one protein described in the  
present invention for the treatment and/or for the  
therapeutic monitoring of a degenerative and/or

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neurological and/or autoimmune disease, preferably multiple sclerosis. These antibodies are polyclonal and preferably monoclonal. Preferably, these antibodies recognize the active site of the protein and, upon  
5 binding, inhibits the function of the protein. The capacity of the antibody to specifically bind to the protein is analyzed by conventional techniques which have been described, such as for example by ELISA or Western blot tests using the natural or synthetic  
10 immunogenic peptide or protein. The antibody titer is determined. The capacity of the antibody to neutralize the function of the protein may be analyzed by various means, for example by determining the reduction in the activity of the immunogenic peptide or protein in the  
15 presence of antibodies, preferably by determining the reduction in the gliotoxic activity using the bioassay test *in vitro*.

For example, the monoclonal antibodies directed against  
20 the target protein or a portion of this protein are produced by conventional techniques used to produce antibodies against surface antigens. Mice or rabbits are immunized (i) either with the natural or recombinant protein of interest, (ii) or with any  
25 immunogenic peptide of this protein of interest, (iii) or with murine cells which express the protein or the peptide of interest and the MHCII molecules.

The Balb/c murine line is the most frequently used. The immunogen is also a peptide chosen from the peptides  
30 defined from the primary sequences of the proteins of interest. For example, the following immunogen was prepared: the peptides SEQ ID Nos. 58, 59, 60 derived from the sequence of the precursor of the ganglioside GM2, the peptides SEQ ID Nos. 61, 62 derived from the  
35 sequence of saposin B and the peptides SEQ ID Nos. 63, 64, 65 derived from calgranulin B were coupled to Keyhole Lymphet hemocyanin, abbreviated peptide-KLH, as support for its use in immunization, or coupled to human serum albumin, abbreviated peptide-HSA. The

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animals were subjected to an injection of peptide-KLH or of peptide-HSA using complete Freund's adjuvant (CFA). The sera and the hybridoma culture supernatants derived from animals immunized with each peptide were  
5 analyzed for the presence of anti-protein antibodies by an ELISA test using the initial proteins. The spleen cells of these mice were consequently recovered and fused with myeloma cells. Polyethylene glycol (PEG) is the fusion agent most frequently used. The hybridomas  
10 producing the most specific and the most sensitive antibodies are selected. The monoclonal antibodies may be produced *in vitro* by cell culture of the hybridomas produced or by recovering murine ascitic fluid after intraperitoneal injection of the hybridomas in mice.  
15 Whatever the mode of production, in supernatant or in ascites, it is then important to purify the monoclonal antibody. The methods of purification used are essentially ion-exchange gel filtration or exclusion chromatography, or even immunoprecipitation. For each  
20 antibody, the method which will make it possible to obtain the best yield should be chosen. A satisfactory number of anti-protein antibodies are targeted in functional tests in order to identify the most efficient antibodies for binding the protein of  
25 interest and/or for blocking the activity of the protein of interest. The monoclonal antibodies selected are humanized by standard "CDR grafting" methods (protocol performed by many companies, as a service). These humanized antibodies may be clinically tested in  
30 the patient. The efficiency of these antibodies may be monitored by clinical parameters.

The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric  
35 antibodies, produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and is also applicable to the present invention.

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Use of molecules inhibiting the proteins of interest identified in the present invention.

The present invention relates to a biological material  
5 for the preparation of pharmaceutical compositions for  
treating mammals suffering from a degenerative and/or  
neurological and/or autoimmune disease, preferably  
multiple sclerosis, said composition comprising  
10 (i) either at least one molecule inhibiting the  
function of at least one protein chosen from the  
proteins identified in the present invention (SEQ ID  
No. 2, 4, 8, 9, 17, 24) and the peptide sequences or  
the fragments of said sequences belonging to the same  
family of proteins chosen from Perlecan, the precursor  
15 of the retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29) and the peptide sequences which exhibit  
20 at least 70% identity, preferably at least 80% identity  
and advantageously at least 98% identity with any one  
of the peptide sequences SEQ ID No. 1 to 29, for  
example inhibiting the gliotoxic activity, (ii) or at  
least one molecule regulating the expression of at  
25 least one protein chosen from the proteins SEQ ID  
No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the  
fragments of said sequences belonging to the same  
family of proteins chosen from Perlecan, the precursor  
of the retinol-binding plasma protein, precursor of the  
30 ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29) and the peptide sequences which exhibit  
at least 70% identity, preferably at least 80% identity  
35 and advantageously at least 98% identity with any one  
of the peptide sequences SEQ ID No. 1 to 29, for  
example to block transcription or translation, (iii) or  
at least one molecule regulating the metabolism of at  
least one protein chosen from the proteins SEQ ID

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No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, (iv) or at least one molecule regulating the expression and/or the metabolism of a ligand for at least one protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, for example a receptor or a cofactor. It is also possible to think that these proteins of the human body can be inhibited with no side effect.

Another important aspect of the invention relates to the identification and the evaluation of the therapeutic efficacy of natural and/or synthetic substances (i) capable of blocking and/or inhibiting the activity of the proteins of interest of the invention and/or of their fragment: SEQ ID No. 2, 4, 8,

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9, 17, 24 and the peptide sequences or the fragments of  
said sequences belonging to the same family of proteins  
chosen from Perlecan, the precursor of the retinol-  
binding plasma protein, precursor of the ganglioside  
5 GM2 activator, calgranulin B and saposin B (for example  
SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)  
and the peptide sequences which exhibit at least 70%  
identity, preferably at least 80% identity and  
10 advantageously at least 98% identity with any one of  
the peptide sequences SEQ ID No. 1 to 29 and/or (ii)  
capable of inhibiting their metabolism such as the  
inhibitors of the corresponding metabolism, the  
inhibitors of enzymes activated by the coenzymes, (iii)  
15 capable of regulating the expression of the proteins of  
interest (SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide  
sequences or the fragments of said sequences belonging  
to the same family of proteins chosen from Perlecan,  
the precursor of the retinol-binding plasma protein,  
20 precursor of the ganglioside GM2 activator, calgranulin  
B and saposin B (for example SEQ ID No. 1, SEQ ID No.  
3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No.  
18 to 23, SEQ ID No. 25 to 29) and the peptide  
sequences which exhibit at least 70% identity,  
25 preferably at least 80% identity and advantageously at  
least 98% identity with any one of the peptide  
sequences SEQ ID No. 1 to 29, (iv) capable of  
inhibiting the function and/or the expression of the  
ligands for the proteins of interest SEQ ID No. 2, 4,  
30 8, 9, 17, 24 and the peptide sequences or the fragments  
of said sequences belonging to the same family of  
proteins chosen from Perlecan, the precursor of the  
retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
35 (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29) and the peptide sequences which exhibit  
at least 70% identity, preferably at least 80% identity  
and advantageously at least 98% identity with any one

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of the peptide sequences SEQ ID No. 1 to 29, such as for example receptors. These substances may be used in prophylactic or therapeutic treatments of the disease. The invention also relates to methods for treating and preventing an autoimmune disease, for example MS, by administering effective quantities of these substances. The substances may be proteins, antibodies, small synthetic or natural molecules, derivatives of the proteins identified in this invention, lipids, glycolipids and the like. The small molecules may be screened and identified in a large quantity using chemical combinatorial libraries. The invention also relates to pharmaceutical compositions comprising these substances in association with acceptable physiological carriers, and methods for the preparation of medicaments to be used in the therapy or in the prevention of autoimmune diseases including MS using these substances.

To identify inhibitory molecules of low molecular weight such as candidate drugs for degenerative and/or neurological and/or autoimmune diseases, such as multiple sclerosis, there are used the tests and protocols described in above and in the patent applications incorporated by way of reference, using samples collected from untreated or treated patients, untreated or treated animal models, or tissues of untreated or treated animal models. This aspect of the invention also includes a method for identifying substances capable of blocking or inhibiting the activity of the proteins of interest, comprising the introduction of these substances into a test *in vitro* or into an animal model *in vivo*. The molecules selected are tested at different concentrations. These inhibitors are also tested in toxicity and pharmacokinetic assays to know if they can represent valid candidate drugs. The substances tested for the inhibition or the blocking of the protein activities or for the expression of the proteins, in these screening

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procedures, may be proteins, antibodies, antibody fragments, small synthetic or natural molecules, derivatives of the proteins of interest and the like. The small molecules may be screened and identified in a large quantity using chemical combinatorial libraries.

By way of example, there may be mentioned as inhibitory substances:

The inhibitors of the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24), the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the inhibitors of the fragments of said proteins. These inhibitors may be included in a prophylactic and therapeutic composition, in particular for the treatment of multiple sclerosis. For example, lycorine, an alkaloid extracted from Amaryllidaceae (e.g.: *Crinum asiaticum*) is used *in vitro* at a concentration of between 0.1 and 0.5 µg/ml and *in vivo* at a concentration of between 0.1 and 1 mg/kg/day. For example, Rolipram (trade name) and Ibudilast (trade name), which are two molecules of the same family of inhibitors of 4(PDE4) phosphodiesterases, are used *in vitro* at concentrations of between 1 and 10 µM/l and *in vivo* at concentrations of between 10 mg/kg/day.

From the amino acid sequences of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same



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family of proteins chosen from Perlecan, the precursor  
of the retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29), it is evident that it is possible to  
deduce the DNA and RNA nucleotide sequences (SEQ ID  
No. 30, 31, 42, 53) corresponding to the proteins of  
interest and the sequences encoding the proteins of the  
10 family of these proteins of interest (for example SEQ  
ID No. 32 to 41, SEQ ID No. 43 to 52, SEQ ID No. 54 to  
57, SEQ ID No. 66 to 67), taking into account the  
genetic code and its degeneracy. Thus, the present  
invention relates to the use of these nucleotide  
15 sequences in the form:

- of antisense sequences,
- of sequences encoding a therapeutic gene,
- 20 - of sequences which may be contained in a vector for  
carrying out cell transformation ex vitro and/or  
in vivo (gene therapy).
- 25 Use of nucleic acids deduced from the amino acid  
sequences of the proteins of interest identified in the  
present invention; antisense nucleic acids and/or  
nucleic acids encoding a therapeutic gene.
- 30 The present invention relates to a biological material  
for the preparation of pharmaceutical compositions for  
treating mammals suffering from a degenerative and/or  
neurological and/or autoimmune disease, in particular  
multiple sclerosis, the composition comprising (i)  
35 either at least one nucleic acid sequence capable of  
hybridizing with a nucleic acid sequence encoding the  
proteins of interest (SEQ ID No. 2, 4, 8, 9, 17, 24)  
and the peptide sequences or the fragments of said  
sequences belonging to the same family of proteins

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chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
5 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their  
10 fragment(s), (ii) or at least one nucleic acid sequence comprising at least one gene of therapeutic interest encoding the proteins or a fragment of proteins (SEQ ID No. 2, 4, 8, 9, 17, 24), the peptide sequences or the fragments of said sequences belonging to the same  
15 family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
20 No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and elements ensuring the expression of said gene *in vivo*  
25 in target cells intended to be genetically modified by said nucleic sequence.

The expression nucleic acid sequence is understood to mean a DNA and/or RNA fragment which is double-stranded  
30 or single-stranded, linear or circular, natural and isolated or synthetic, designating a precise succession of nucleotides, modified or otherwise, which makes it possible to define a fragment or a region of a nucleic acid chosen from the group consisting of a cDNA; a  
35 genomic DNA; a plasmid DNA; a messenger RNA. These nucleic acid sequences are deduced from the amino acid sequence of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins

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chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, using the genetic code. Because of the degeneracy of the genetic code, the invention also encompasses equivalent or homologous sequences. These defined sequences allow persons skilled in the art themselves to define the appropriate nucleic acids.

Accordingly, the present invention relates to a biological material for the preparation of pharmaceutical compositions comprising at least one nucleic acid sequence capable of hybridizing with a nucleic acid sequence encoding the proteins of interest or their fragment(s) (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

The invention consists in defining and using nucleic acid molecules complementary to the DNA and/or RNA sequences encoding the proteins of interest or their fragment(s). These fragments correspond to ribozyme or antisense molecules and may be synthesized using automated synthesizers, such as those marketed by the

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company Applied Biosystem. The invention describes the use of these nucleic acids capable of hybridizing under stringent conditions with the DNA and/or RNA encoding the proteins of the invention or their fragment(s).

5 Characteristic stringency conditions are those which correspond to a combination of the temperature and of the saline concentration chosen approximately between 12 and 20°C under the T<sub>m</sub> ("melting temperature") of the hybrid under study. Such molecules are synthesized and  
10 may be labeled using conventional labeling methods used for molecular probes, or may be used as primers in amplification reactions. The sequences which exhibit at least 90% homology relative to a reference sequence also form part of the invention, as well as the  
15 fragments of these sequences which have at least 20 nucleotides and preferably 30 contiguous nucleotides that are homologous with respect to a reference sequence. To reduce the proportion of natural or variant peptides, it is possible to envisage an  
20 antisense and/or ribozyme approach. Such an approach is widely described in the literature. Of course, such antisense molecules may constitute, as such, vectors. It is also possible to use vectors which comprise a nucleic acid sequence which encodes an antisense.

25

The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from a degenerative and/or neurological and/or autoimmune disease, such as  
30 multiple sclerosis, said composition comprising at least one nucleic acid sequence containing at least one gene of therapeutic interest and elements ensuring the expression of said gene *in vivo* in target cells intended to be genetically modified by said nucleic  
35 sequence.

These nucleic acid sequences and/or vectors (antisense or encoding a protein or a fragment of a protein) make it possible to target the cells in which the peptide is

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expressed, such as macrophage cells: (i) either by the use of a targeting molecule introduced on the vector, (ii) or by the use of a particular property of these cells.

5

Use of vectors comprising a gene of therapeutic interest corresponding to the genes for the proteins of interest identified in the present invention.

10 The present invention relates to a biological material for the preparation of pharmaceutical compositions for preventing and treating degenerative and/or neurological and/or autoimmune diseases, such as multiple sclerosis, the composition comprising a  
15 nucleic acid sequence comprising a gene of therapeutic interest and elements for expressing said gene of interest. The genes may be nonmutated or mutated. They may also consist of nucleic acids modified such that it is not possible for them to integrate into the genome  
20 of the target cell, or of nucleic acids stabilized with the aid of agents, such as spermine.

Such a gene of therapeutic interest encodes in particular:

25

(i) either at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same  
30 family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
35 No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s),

(ii) or at least all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein or a protein fragment chosen from the proteins  
5 identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the  
10 ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity  
15 and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. This may include in particular a native transmembrane antibody, or a fragment or derivative of such an antibody, as long as said antibody, antibody fragment or derivative  
20 is expressed at the surface of the genetically modified target cell of the mammal and is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte involved in the process for activating such a cell,

25

(iii) or at least one molecule inhibiting at least one protein or its fragments, said protein being chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of  
30 said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
35 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29; the proteins

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inhibiting the function and/or the metabolism and/or the binding of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins  
5 chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)  
10 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29,

15 (iv) or at least one ligand or any portion of a ligand capable of binding to at least one protein or one protein fragment chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging  
20 to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No.  
25 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and/or of inhibiting its  
30 function.

More particularly, the expression antibody fragment is understood to mean the F(ab)<sub>2</sub>, Fab', Fab, sFv fragments (Blazar et al., 1997, Journal of Immunology 159: 5821-  
35 5833; Bird et al., 1988 Science 242: 423-426) of a native antibody and the expression derivative is understood to mean, for example, a chimeric derivative of such an antibody (see for example the chimeras of the Mouse/Human anti-CD3 antibodies in Arakawa et al.,

1996 J Biochem 120: 657-662 or the immunotoxins such as sFv-toxin by Chaudary et al 1989, Nature 339: 394-397). The expression transmembrane antibody is understood to mean an antibody in which at least the functional  
5 region capable of recognizing and binding to its specific antigen is expressed at the surface of the target cells in order to allow said recognition and binding. More particularly, the antibodies according to the present invention consist of fusion polypeptides  
10 comprising the amino acids defining said functional region and an amino acid sequence (transmembrane polypeptide) allowing anchoring within the membrane lipid double layer of the target cell or at the outer surface of this bilayer. The nucleic sequences encoding  
15 numerous transmembrane polypeptides are described in the literature. According to a most advantageous case, the nucleic acid sequence encoding the antibody heavy chain is fused with the nucleic acid sequence encoding the said transmembrane polypeptide.

20

The expression elements ensuring the expression of said gene *in vivo* refers in particular to the elements necessary to ensure the expression of said gene after its transfer into a target cell. This includes in  
25 particular promoter sequences and/or regulatory sequences which are efficient in said cell, and optionally the sequences required to allow expression at the surface of the target cells of said polypeptide. The promoter used may be a viral, ubiquitous or tissue-specific promoter or a synthetic promoter. By way of  
30 example, there may be mentioned promoters such as the promoters of the viruses RSV (Rous Sarcoma Virus), MPSV, SV40 (Simian Virus), CMV (Cytomegalovirus) or of the vaccinia virus, the promoters of the gene encoding  
35 muscle creatine kinase, actin. It is, in addition, possible to choose a promoter sequence specific for a given cell type, or activable under defined conditions. The literature provides a large amount of information relating to such promoter sequences.





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nucleic acid sequence may be in the form of a "vector" and more particularly in the form of a viral vector, such as, for example, an adenoviral vector, a retroviral vector, a vector derived from a poxvirus, in particular derived from the vaccinia virus or from the Modified Virus Ankara (MVA) or from a nonviral vector such as, for example, a vector consisting of at least one said nucleic acid sequence complexed or conjugated with at least one carrier molecular substance selected from the group consisting of a cationic amphiphile, in particular a cationic lipid, a cationic or neutral polymer, a practical polar compound chosen in particular from propylene glycol, polyethylene glycol, glycerol, ethanol, 1-methyl-L-2-pyrrolidone or their derivatives, and an aprotic polar compound chosen in particular from dimethyl sulfoxide (DMSO), diethyl sulfoxide, di-n-propyl sulfoxide, dimethyl sulfone, sulfolane, dimethylformamide, dimethylacetamide, tetramethylurea, acetonitrile or their derivatives. The literature provides a large number of examples of such viral and nonviral vectors.

Such vectors may in addition and preferably comprise targeting elements which can make it possible to direct the transfer of a nucleic acid sequence toward certain cell types or certain particular tissues such as cytotoxic cells and antigen-presenting cells). They can also make it possible to direct the transfer of an active substance toward certain preferred intracellular compartments such as the nucleus, the mitochondria or the peroxisomes, for example. This may also include elements facilitating penetration into the cell or the lysis of intracellular compartments. Such targeting elements are widely described in the literature. This may include, for example, all or part of lectins, peptides, in particular the peptide JTS-1 (see PCT patent application WO 94/40958), oligonucleotides, lipids, hormones, vitamins, antigens, antibodies, ligands specific to membrane receptors, ligands capable

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of acting with an antiligand, fusogenic peptides, nuclear localization peptides or a composition of such compounds.

5 Use of cells transformed *in vivo* after injection of  
vectors containing at least one gene of therapeutic  
interest defined from the proteins of interest  
identified in the present invention (SEQ ID No. 2, 4,  
8, 9, 17, 24) and the peptide sequences or the  
10 fragments of said sequences belonging to the same  
family of proteins chosen from Perlecan, the precursor  
of the retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
15 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29) and the peptide sequences which exhibit  
at least 70% identity, preferably at least 80% identity  
and advantageously at least 98% identity with any one  
of the peptide sequences SEQ ID No. 1 to 29.

20

The present invention relates to a biological material  
for the preparation of pharmaceutical compositions for  
preventing and treating mammals suffering from  
degenerative and/or neurological and/or autoimmune  
25 diseases, preferably multiple sclerosis, the  
composition comprising at least one vector containing a  
therapeutic gene as described below, capable of being  
introduced into a target cell *in vivo* and of expressing  
the gene of therapeutic interest *in vivo*. The advantage  
30 of this invention consists in the possibility of  
maintaining long term a basal level of molecules  
expressed in the patient treated. Vectors or nucleic  
acids encoding genes of therapeutic interest are  
injected. These vectors and nucleic acids should be  
35 transported up to the target cells and transfect these  
cells in which they have to be expressed *in vivo*.

The invention relates to the expression *in vivo* of  
nucleotide sequences and/or vectors as designated in

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the preceding paragraph, that is to say sequences corresponding to genes of therapeutic interest encoding in particular:

- 5 (i) either at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor  
10 of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit  
15 at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s),
- 20 (i) or at least all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said  
25 sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
30 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. This may  
35 include a native transmembrane antibody, or a fragment or derivative of such an antibody, as long as said antibody or antibody fragment or derivative is expressed at the surface of the genetically modified target mammalian cell and in that said antibody is

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capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte and involved in the process of activating such a cell. This may include antibody fragments  
 5 expressed by cells capable of secreting said antibodies in the bloodstream of a mammal or patient carrying the cells genetically modified by the gene encoding the antibody,

10 (ii) or at least one molecule inhibiting at least one protein chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor  
 15 of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit  
 20 at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29; protein inhibiting the function and/or metabolism and/or binding of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24  
 25 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example  
 30 SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of  
 35 the peptide sequences SEQ ID No. 1 to 29,

(iii) or at least one ligand or any portion of the ligand capable of binding to at least one protein chosen from the proteins identified (SEQ ID No. 2, 4,

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8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and/or of inhibiting its function.

According to a particular embodiment, this includes using gene therapy so as to direct the immune response against the target protein, peptide or molecule of interest, that is to say against any protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, their fragment(s) and/or against any molecule inhibiting the function and/or expression and/or metabolism of said proteins of interest, and/or ligands of said proteins such as, for example, the receptors. For that, it is evident that the cells to be targeted for the transformation with a vector are cells belonging to the immune system, either lymphocyte-type cells (CD4/CD8), or antigen-presenting cells (dendritic cells, macrophages and the like).

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According to a particular embodiment, the antigen-presenting cells (APC) are genetically modified, in particular *in vivo*. APCs such as macrophages, dendritic cells, microgliocytes and astrocytes play a role in  
5 initiating the immune response. They are the first cellular components which capture the antigen, prepare it in the cell and express the transmembrane MHC I and MHC II molecules involved in presenting the immunogen to the CD4+ and CD8+ T cells, they produce specific  
10 secondary proteins which participate in activating the T cells (Debrick et al., 1991, J. Immunol 147: 2846; Reis et al., 1993, J Ep Med 178: 509; Kovacsovics-bankowski et al., 1993, PNAS 90: 4942; Kovacsovics-bankowski et al., 1995 Science 267: 243; Svensson et  
15 al., 1997, J Immunol 158: 4229; Norbury et al., 1997, Eur J Immunol 27: 280). For a vaccination, it may be advantageous to have a gene therapy system which can target the gene transfer into such APC cells, that is to say a gene which encodes a polypeptide which can,  
20 after its intracellular production and its "processing", be presented to the CD8+ and/or CD4+ cells by the molecules of the MHC I and MHC II complexes, respectively, at the surface of these cells.

25 It is chosen to express at the surface of the APC cells *in vivo* all or part of an antibody and/or of a ligand such as, for example, a receptor, capable of reacting with the target protein or peptide chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide  
30 sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID  
35 No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide

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sequences SEQ ID No. 1 to 29. Such cells will then specifically phagocytose said protein or said peptide, the "processer" so that fragments of this peptide are present at the surface of the antigen-presenting cells.

5

The literature provides a large number of examples of genes encoding antibodies capable of reacting with polypeptides or receptors. It is within the capability of persons skilled in the art to obtain the nucleic acid sequences encoding such antibodies. There may be mentioned, for example, the genes encoding the light and heavy chains of the antibody YTH 12.5 (anti-CD3) (Routledge et al. 1991, Eur J Immunol 21: 2717-2725), of the anti-CD3 according to Arakawa et al; 1996, J. Biochem. 120: 657-662. The nucleic acid sequences of such antibodies are easily identifiable from the databases commonly used by persons skilled in the art. It is also possible, starting with hybridomas available from ATCC, to clone the nucleic acid sequences encoding the heavy and/or light chains of these various antibodies by amplification methods such as RT-PCR with the aid of specific oligonucleotides or techniques using cDNA libraries (Maniatis et al., 1982, Molecular cloning. A laboratory manual CSH Laboratory, Cold Spring Harbor, New York). The sequences thus cloned are then available for their cloning into vectors. According to a preferred case of the invention, the nucleic acid sequence encoding the heavy chain of the antibody is fused by homologous recombination with the nucleic acid sequence encoding a transmembrane polypeptide such as the rabies glycoprotein or gp160 (Polydefkis et al., 1990, J Exp Med 171: 875-887). These molecular biology techniques have been fully described.

35

It is chosen to express at the surface of the APC cells *in vivo* immunogenic fragments corresponding to at least one proteins chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments



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of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. For that, it is possible to choose to cause the vector to express either the full-length polypeptide or, preferably, polypeptides selected to react with specific ligands and/or receptors. The immunogenic peptide encoded by the polynucleotide introduced into the cell of the vertebrate *in vivo* may be produced and/or secreted, made ready and then presented to an antigen-presenting cell (APC) in the context of the molecules of the MHC. The APCs thus transferred *in vivo* induce an immune response directed against the immunogen expressed *in vivo*. The APCs possess different mechanisms for capturing the antigens: (a) capture of the antigens by membrane receptors such as the receptors for immunoglobulins (Fc) or for the complement which are available at the surface of the granulocytes, monocytes or macrophages allowing efficient delivery of the antigen into the intracellular compartments after phagocytosis mediated by the receptors. (b) entry into the APCs by pinocytosis in fluid phase, involving various mechanisms: micropinocytosis, that is to say the capture of small vesicles (0.1  $\mu\text{m}$ ) by the clathrin-coated pits, and macropinocytosis, that is to say the capture of larger vesicles (with a size varying graft 0.5  $\mu\text{m}$  and about 6  $\mu\text{m}$ ) (Sallusto et al. 1995, J Exp Med 182: 389-400). While micropinocytosis constitutively exists in all cells, macropinocytosis is limited to cellular types such as, for example, the macrophages, dendritic cells, astrocytes, epithelial cells stimulated by growth factors (Racoosin et al., J Cell

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Sci 1992, 102: 867-880). In this invention, the expression cells capable of macropinocytosis is understood to mean the cells which can carry out the events described above and the cells which can capture  
5 macromolecules preferably between 0.5  $\mu$ m and about 6  $\mu$ m in the cytoplasm.

According to a particular embodiment, the cytotoxic effector cells or the helper T lymphocytes are  
10 genetically modified in particular *in vivo* so that they express at their surface a polypeptide corresponding to the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from  
15 Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the  
20 peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, ligands for said proteins, which are naturally not expressed by these  
25 cells and which are capable of inducing the process of activation of such cells, by introducing into these cells nucleic acid sequences containing the gene encoding such a polypeptide. In accordance with the present invention, it is also possible to select a  
30 nucleic acid sequence containing a gene of therapeutic interest encoding all or part of an antibody directed against a protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same  
35 family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID

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No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, capable of  
5 being expressed at the surface of the target cells of the patient to be treated, said antibody being capable of binding to a polypeptide which is naturally not expressed by these cytotoxic effector cells or helper T lymphocytes.

10

The expression cytotoxic effector cells is understood to designate the macrophages, astrocytes, cytotoxic T lymphocytes (CTL) and killer (NK) cells as well as their derivatives such as, for example, LAKs (Versteeg  
15 1992 Immunology today 13: 244-247; Brittende et al 1996, Cancer 77: 1226-1243). The expression "helper T lymphocytes" is understood to designate in particular the CD4 cells which allow, after activation, the secretion of factors for activating the effector cells  
20 of the immune response. The polypeptides, and in particular the receptors expressed at the surface of these cells and which are involved in the activation of such cells, constitute in particular all or part of the TCR complex or CD3, all or part of the CD8, CD4, CD28, LFA-1, 4-1BB (Melero et al., 1998, Eur J Immunol 28:  
25 1116-1121), CD47, CD2, CD1, CD9, CD45, CD30 and CD40 complexes, all or part of the cytokine receptors (Finke et al., 1998, Gene therapy 5: 31-39), such as IL-7, IL-4, IL-2, IL-15 or GM-CSF, all or part of the  
30 receptor complex for the NK cells such as for example NKAR, Nkp46, and the like; (Kawano et al., 1998 Immunology 95: 5690-5693; Pessino et al., 1998 J Exp Med 188: 953-960), Nkp44, all or part of the macrophage receptors such as for example the Fc receptor (Deo et al., 1997, Immunology Today 18: 127-135).  
35

Numerous tools have been developed for introducing various heterologous genes and/or vectors into cells, in particular mammalian cells. These techniques may be

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divided into two categories: the first category involves physical techniques such as microinjection, electroporation or particle bombardment. The second category is based on the use of molecular and cell  
5 biology techniques with which the gene is transferred with a biological or synthetic vector which facilitates the introduction of the material into the cell in vivo. Nowadays, the most efficient vectors are the viral, in particular adenoviral and retroviral, vectors. These  
10 viruses possess natural properties for crossing the plasma membranes, avoiding degradation of their genetic material and introducing their genome into the nucleus of the cell. These viruses have been widely studied and some are already experimentally used in human  
15 applications in vaccination, immunotherapy, or to compensate for genetic deficiencies. However, this viral approach has limitations, in particular due to the restricted cloning capacity in these viral genomes, the risk of disseminating the viral particles produced  
20 in the body and the environment, the risk of artefactual mutagenesis by insertion into the host cell in the case of retroviruses, and the possibility of inducing a high inflammatory immune response in vivo during the treatment, which limits the number of  
25 injections possible (McCoy et al. 1995, Human Gene Therapy 6: 1553-1560; Yang et al., 1996 Immunity 1: 433-422). Other alternative systems to these viral vectors exist. The use of nonviral methods such as, for example, coprecipitation with calcium phosphate, the  
30 use of receptors which mimic the viral systems (for a summary see Cotten and Wagner 1993, Current Opinion in Biotechnology, 4: 705-710), or the use of polymers such as polyamidoamines (Haensler and Szoka 1993, Bioconjugate Chem 4: 372-379). Other nonviral  
35 techniques are based on the use of liposomes whose efficiency for the introduction of biological macromolecules such as DNA, RNA, proteins or active pharmaceutical substances has been widely described in the scientific literature. In this domain, teams have

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proposed the use of cationic lipids having a high affinity for the cell membranes and/or nucleic acids. Indeed, it has been shown that a nucleic acid molecule itself could cross the plasma membrane of some cells  
5 *in vivo* (WO 90/11092), the efficiency depending in particular on the polyanionic nature of the nucleic acid. Since 1989 (Felgner et al., Nature 337: 387-388), cationic lipids have been proposed to facilitate the introduction of large anionic molecules, which  
10 neutralizes the negative charges on these molecules and promotes their introduction into the cells. Various teams have developed such cationic lipids: DOTMA (Felgner et al., 1987, PNAS 84: 7413-7417), DOGS or Transfectam<sup>TM</sup> (Behr et al., 1989, PNAS 86: 6982-6986),  
15 DMRIE and DORIE (Felgner et al., 1993 methods 5: 67-75), DC-CHOL (Gao and Huang 1991, BBRC 179: 280-285), DOTAP<sup>TM</sup> (McLachlan et al., 1995, Gene therapy 2: 674-622) or Lipofectamine<sup>TM</sup>, and the other molecules described in patents WO9116024, WO9514651, WO9405624.  
20 Other groups have developed cationic polymers which facilitate the transfer of macromolecules, in particular anionic macromolecules, into cells. Patent WO95/24221 describes the use of dendritic polymers, the document WO96/02655 describes the use of  
25 polyethyleneimine or polypropyleneimine and the documents US-A-5595897 and FR 2719316, the use of polylysine conjugates.

Given that it is desired to obtain *in vivo* a  
30 transformation targeted toward a given cell type, it is evident that the vector used should be able to be "targeted" itself, as described above.

Use of cells transformed *in vitro* or *ex vivo* with  
35 vectors containing a gene of therapeutic interest defined in relation to the proteins of interest identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same

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family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

10

The present invention relates to a biological material for the preparation of pharmaceutical compositions for preventing and treating degenerative and/or neurological and/or autoimmune diseases, preferably  
15 multiple sclerosis, the composition comprising at least one cell, in particular a cell not naturally producing antibodies, in a form allowing their administration into the body of a mammal, human or animal, as well as optionally their prior culture, said cell being  
20 genetically modified *in vitro* by at least one nucleic acid sequence containing at least one gene encoding *in vivo*:

(i) at least one protein chosen from the proteins  
25 SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin  
30 B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at  
35 least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98%

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identity with any one of the peptide sequences SEQ ID No. 1 to 29, and any fragment,

(ii) at least one peptide defined from the primary  
5 sequence of at least one protein chosen from the  
proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide  
sequences or the fragments of said sequences belonging  
to the same family of proteins chosen from Perlecan,  
the precursor of the retinol-binding plasma protein,  
10 precursor of the ganglioside GM2 activator, calgranulin  
B and saposin B (for example SEQ ID No. 1, SEQ ID  
No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID  
No. 18 to 23, SEQ ID No. 25 to 29) and the peptide  
sequences which exhibit at least 70% identity,  
15 preferably at least 80% identity and advantageously at  
least 98% identity with any one of the peptide  
sequences SEQ ID No. 1 to 29,

(iii) at least any molecule inhibiting the function  
20 and/or binding and/or expression of these proteins,

(iv) at least one peptide derived from the primary  
sequence of a protein chosen from the proteins SEQ ID  
No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the  
25 fragments of said sequences belonging to the same  
family of proteins chosen from Perlecan, the precursor  
of the retinol-binding plasma protein, precursor of the  
ganglioside GM2 activator, calgranulin B and saposin B  
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5  
30 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID  
No. 25 to 29) and the peptide sequences which exhibit  
at least 70% identity, preferably at least 80% identity  
and advantageously at least 98% identity with any one  
of the peptide sequences SEQ ID No. 1 to 29, and  
35 capable of binding to at least one glycoprotein of the  
MHCI,

(v) at least any antibody and any portion of antibody  
which are capable of binding to at least one protein

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chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24,  
and the peptide sequences or the fragments of said  
sequences belonging to the same family of proteins  
chosen from Perlecan, the precursor of the retinol-  
5 binding plasma protein, precursor of the ganglioside  
GM2 activator, calgranulin B and saposin B (for example  
SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID  
No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)  
and the peptide sequences which exhibit at least 70%  
10 identity, preferably at least 80% identity and  
advantageously at least 98% identity with any one of  
the peptide sequences SEQ ID No. 1 to 29.

More particularly, said target cell is obtained either  
15 from the mammal to be treated, or from a mammal other  
than that to be treated. In the latter case, it should  
be noted that said target cell will have undergone a  
treatment making it compatible with the mammal to be  
treated. The expression "mammal" is preferably  
20 understood to mean a human mammal. These cells are  
established as cell lines and are preferably MHCII+ or  
MHCII+-inducible such as the lymphocytes, monocytes,  
astrocytes and oligodendrocytes.

25 The invention also relates to the modified cells and to  
a method for preparing a cell as described above,  
characterized in that there is introduced into a  
mammalian cell not naturally producing antibodies, by  
any appropriate means, at least one nucleic acid  
30 sequence containing at least one gene of therapeutic  
interest and elements ensuring the expression of said  
gene in said cell, said gene of therapeutic interest  
containing a nucleic acid sequence encoding a molecule  
or a molecule fragment *in vivo*, as described  
35 immediately above. More particularly, it relates to  
prokaryotic cells, yeast cells and animal cells, in  
particular mammalian cells transformed with at least  
one nucleotide sequence and/or one vector as described  
above.



According to a particular embodiment, the cells (dendritic cells, macrophages, astrocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, and the like) of the patient or allogenic cells are placed in contact with a purified preparation of the target polypeptide, the latter being internalized, made ready and presented at the cell surface associated with the MHCI and/or MHCII molecules and thus to induce a specific immune response against the peptide. The "activated" cells are then administered to the patient in whom they will induce an immune response specific for the antigens (a natural route is used for the immune response, but what the antigen-presenting cell is going to present is checked).

According to a particular embodiment, the antigen-presenting cells (dendritic cell, macrophage, astrocytes, and the like) are modified *in vitro* in order to express the antigens in the transformed cell which will associate with the MHCI and/or MHCII molecules and be presented at the surface of the cells to induce a perfectly targeted immune reaction in the patient in whom the modified cell is administered.

All the vaccine approaches are not always satisfactory and lead, for example, to limited immune reactions directed solely against immunodominant epitopes or against antigens exhibiting great variability. Likewise, the incorrect presentation of the antigens by the glycoproteins of the MHC system at the surface of the cells does not make it possible to develop in the treated patient a suitable anti-protein of interest immunity. To overcome these problems, some authors have proposed, in the context of such vaccine methods, to select the antigenic minimal fragments corresponding to the peptide portions capable of being specifically recognized by the cytotoxic T lymphocytes, expressing them in the cells so that they associate with the

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molecules of the MHCI and are presented at the surface of the cells in order to induce a perfectly targeted immune reaction in the treated patient (Toes et al. 1997, PNAS 94: 14660-14665). More particularly, it has  
5 been shown that epitopes of very small sizes (varying from 7 to about 13 amino acids), which are expressed from minigenes introduced into a vaccinia virus, could induce a cellular type immunization. It has moreover been shown that several minigenes could be conjointly  
10 expressed starting with the same vector (this particular construct is called "string of beads"). Such a construct has the advantage of inducing a synergistic CTL-type immune reaction (Whitton et al., 1993 J. of Virology 67: 348-352).

15

Protocol for bringing the cells and the antigenic fragment into contact:

The presentation of the antigenic fragments by the MHCI  
20 molecules depends on an identified intracellular method (see Groettrup et al., 1996 Immunology Today 17: 429-435 for a review) in which very short antigenic peptides (about 7-13 amino acids) are produced by degradation of a more complex polypeptide against which  
25 the final immune reaction will be directed. These short peptides are then combined with the MHCI or MHCII molecules to form a protein complex which is transported to the cell surface in order to present said peptides to the circulating cytotoxic T  
30 lymphocytes or to the circulating helper T lymphocytes, respectively. It should be noted, in addition, that the specificity of the MHCI or MHCII molecules toward the antigenic peptides varies as a function of the MHCI or MHCII molecules (example for MHCI: HLA-A, HLA-B, and  
35 the like) and the allele (example for MHCI: HLA-A2, HLA-A3, HLA-A11) which are considered. Within the same animal species, from one individual to another, there is great variability of the genes encoding the molecules of the MHC system (on this subject, see in

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particular George et al., 1995, Immunology Today 16: 209-212).

According to a particular embodiment, the cells, such  
 5 as dendritic cells, macrophages, astrocytes, CD4+  
 T lymphocytes, CD8+ T lymphocytes, are modified so as  
 to express at their surface antibodies specific for the  
 targeted peptide. The peptide is neutralized with the  
 antibodies expressed at the surface of the cells. These  
 10 cells are preferably immune cells, preferably from the  
 patient, are preferably cytotoxic and modified to  
 express all or part of an antibody specific for the  
 target polypeptide.

15 Isolation of mononucleated cells from peripheral blood:

In 1968, Boyum described a rapid technique which makes  
 it possible, by centrifugation of blood on a density  
 gradient, to separate the mononucleated cells  
 20 (lymphocytes and monocytes) with a good yield  
 (theoretical yield 50%, that is to say  $10^6$  cells/ml of  
 blood). 50 ml of peripheral blood sterilely collected  
 in heparinized tubes are centrifuged for 20 minutes at  
 150 g at 20°C. The cells recovered are diluted in two  
 25 volumes of initial peripheral blood of sterile PBS.  
 10 ml of this suspension are deposited on 3 ml of a  
 Ficoll-Hypaque solution (medium for separation of the  
 lymphocytes, Flow). After centrifuging for 20 minutes  
 at 400 g and 20°C without decelerating braking, the  
 30 mononucleated cells sediment at the PBS-Ficoll  
 interface, as an opalescent dense layer, whereas  
 practically all the red blood cells and the polynuclear  
 cells sediment at the bottom of the tube. The mono-  
 nucleated cells are recovered and washed with sterile  
 35 PBS.

Internalization of the antigens by the antigen-  
 presenting cells:

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Prior treatment of the antigen-presenting cells: the antigen-presenting cells are washed beforehand with PBS buffer containing 0.5% (w/v) BSA, then counted and they are then preincubated in the presence of various reduction inhibitors three times in PBS-0.5% BSA containing 10  $\mu$ M to 10 mM final of DTNB (5,5'-dithio-bis-2-nitrobenzoic acid) or NEM (N-ethylmaleimide). The subsequent stages of binding of antigens to the cell surface or of internalization of antigens are also carried out in the presence of various concentrations of inhibitors.

Protocol for internalization of the antigens by the antigen-presenting cells:

8  $\times$  10<sup>6</sup> cells are internalized in the presence of saturating quantity of proteins radiolabeled with iodine 125 (1  $\mu$ g) in microwells in 70  $\mu$ l. After incubating for one hour at 4°C, with stirring, the antigens are bound to the surface of the cells. The cell suspension is washed twice in PBS-BSA and the cellular pellets are taken up in 70  $\mu$ l of buffer and incubated at 37°C for various periods ranging up to 2 hours. Cells and supernatants are separated by centrifugation at 800 g for 5 minutes 4°C. For longer incubation periods, the preliminary stage of prebinding of the antigens to the surface of the cells is eliminated. The cells are diluted in RPMI-10% FCS medium in the presence of 20 mM Hepes, at 10<sup>6</sup> cells/ml. The cells are incubated in the presence of an excess of antigen for various periods at 37°C (1  $\mu$ g of molecules/ 5  $\times$  10<sup>7</sup> monocyte/macrophage cells or 10<sup>8</sup> B-EBV cells).

All the therapeutic agents defined in the context of the present invention are used for preventing and/or treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, alone or in combination. They may also be used to evaluate their efficacy *in vitro* or *in vivo*.

## Administration of therapeutic agents in humans:

The biological material according to the invention may  
5 be administered *in vivo* in particular in injectable  
form. It is also possible to envisage injection by the  
epidermal, intravenous, intraarterial, intramuscular or  
intracerebral route with a syringe or any other  
equivalent means. According to another embodiment, by  
10 oral administration or any other means perfectly known  
to a person skilled in the art and applicable to the  
present invention. The administration may take place as  
a single dose or as a dose repeated once or several  
times after a certain time interval. The most  
15 appropriate route of administration and dosage vary as  
a function of various parameters such as, for example,  
the individual or the disease to be treated, the stage  
and/or the progression of the disease, or alternatively  
the nucleic acid and/or protein and/or peptide and/or  
20 molecule and/or cell to be transferred or the target  
organ/tissue.

To carry out the treatment of the mammal mentioned in  
the present invention, it is possible to have  
25 pharmaceutical compositions comprising a biological  
material as described above, advantageously combined  
with a pharmaceutically acceptable vehicle for  
administration to humans or to animals. The use of such  
carriers is described in the literature (see, for  
30 example, Remington's Pharmaceutical Sciences 16th ed.  
1980, Mack Publishing Co). This pharmaceutically  
acceptable vehicle is preferably isotonic, hypotonic or  
exhibits low hypertonicity and has a relatively low  
ionic strength, such as for example a sucrose solution.  
35 Moreover, said composition may contain solvents,  
aqueous or partially aqueous vehicles such as sterile  
water, free of pyrogenic agents and dispersion media  
for example. The pH of these pharmaceutical

compositions is suitably adjusted and buffered according to conventional techniques.

**Figures:**

5

Figure 1 represents the amino acid sequence of the GM2AP protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-GM2AP peptides antibodies.

10

Figure 2 represents the amino acid sequence of the MRP14 protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-MRP14 peptides antibodies.

15

Figure 3 represents the amino acid sequence of the Saposin B protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-Saposin B peptides antibodies.

20

Figure 4 represents the assay of the MRP8 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

25

Figure 5 represents the assay of the MRP14 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

30

Figure 6 represents the assay of the MRP8/14 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of

35

patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

5

Figure 7 represents the mean concentrations of the MRP8, MRP14 and MRP8/14 proteins (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from  
10 other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

Figure 8 represents the assay of the GM2AP protein  
15 (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per  
20 category. MS means multiple sclerosis, OND means other neurological diseases and Healthy means samples from controls supposed healthy (HC).

Figure 9 represents the assay of the Saposin B protein  
25 ( $\mu$ g/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per  
30 category. MS means multiple sclerosis, OND means other neurological diseases and Healthy means samples from controls supposed healthy (HC).

Figure 10 represents the codetection of the Saposin B  
35 ( $\mu$ g/ml - on the y-axis) and GM2AP (ng/ml - on the x-axis) proteins in urine samples from MS patients, controls supposed healthy and patients suffering from other neurological diseases and the correlation observed between the levels of the two proteins.

Figure 11 represents: figure 11A, the assay of the GM2AP protein in ng/ml in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve); figure 11B, the assay of the Saposin B protein in  $\mu\text{g/ml}$  in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 12 represents the product of the concentrations of the GM2AP and saposin B proteins in  $\text{ng}\times\mu\text{g/ml}^2$  in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 13 represents: figure 13A, the assay of the GM2AP protein in ng/ml in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve); figure 13B, the assay of the Saposin B protein in  $\mu\text{g/ml}$  in the urine of an MS patient in progressive form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 14 represents the product of the concentrations of the GM2AP and saposin B proteins in  $\text{ng}\times\mu\text{g/ml}^2$  in the urine of an MS patient in progressive form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 15 represents the correlation between the concentrations of GM2AP in ng/ml (x-axis) and



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gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

5 Figure 16 represents the correlation between the concentrations of Saposin B in  $\mu\text{g/ml}$  (x-axis) and gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

10 Figure 17 represents the correlation between the product of the concentrations of GM2AP and Saposin B in  $\text{ng} \times \mu\text{g/ml}^2$  (x-axis) and gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

Figure 18 represents the correlation between the concentrations of GM2AP ( $\text{ng/ml}$  - on the left-hand y-axis), the concentrations of Saposin B ( $\mu\text{g/ml}$  - right-hand y-axis) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (x-axis). Two estimated correlation straight lines are represented on the graph. The lines in bold relate to the concentrations of saposin B; the lines in light black relate to the concentrations of GM2AP.

### Examples:

#### Example 1: Collecting and pooling of urines

30 Urine samples of different volumes were collected from healthy individuals (MS-negative) having a priori no neurological or autoimmune disease. The toxic activity of each sample toward murine astrocyte cells was tested *in vitro* using the MTT test. In total, a pool of 20 liters of urine was formed (MS-negative pool). In parallel, urine samples of different volumes were collected from individuals suffering from multiple sclerosis (MS-positive) at various stages of the

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disease. The toxic activity of each sample toward murine astrocyte cells was tested *in vitro* using the MTT test. In total, a pool of 80 liters of urine was formed (MS-positive pool).

5

#### Example 2: Purification of the urinary proteins

The pools of MS-positive and MS-negative urine, collected and tested according to example 1, were  
10 purified in order to obtain a high protein concentration and to remove the high molecular weight proteins as far as possible.

Precipitation: precipitations with ammonium sulfate  
15 (Prolabo - ref. 21 333 365) were carried out on the pools of MS-positive and MS-negative urine. The percentage of 60% saturated ammonium sulfate per 40% of urine, that is 390 grams of ammonium sulfate per liter of urine, was used. Each pool was distributed into  
20 fractions of 1.8 liters in 2-liter bottles in order to improve the precipitation. The precipitation was carried out for 2 x 8 hours, at room temperature, with gentle stirring. After centrifugation of the pools of urine at 3 000 rpm for 10 min, at a temperature of  
25 10°C, the pellet obtained is taken up in 20 mM Tris buffer containing 1 mM CaCl<sub>2</sub> and 0.25 M urea. The mixture was then centrifuged at 3 000 rpm for 10 min. The supernatant contains the concentrated proteins. It is either used immediately for the next stage, or  
30 frozen if the next stage cannot be performed continuously.

Ion-exchange chromatography: the solution containing the proteins was then passed over a DEAE fast Flow gel  
35 (marketed by PHARMACIA). This stage is carried out at low pressure on a PHARMACIA column filled with gel. The buffers are brought to the column by a peristaltic pump which allows a uniform flow rate. The buffer for equilibrating the column is 20 mM Tris buffer, pH 7.

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The fraction corresponding to the precipitation supernatant and containing an excessively high quantity of salts is dialyzed against this buffer before depositing on the column. Elution with a salt gradient  
5 makes it possible to recover the proteins. The elution gradient is performed in steps of 100, 200, 300, 500 mM NaCl in the buffer for equilibrating the column. The elution fractions are tested by the MTT test and only the positive fractions, that is the fraction eluted at  
10 200 mM NaCl, will be preserved. These fractions may be immediately treated or stored in the freeze-dried state.

Purification: steric exclusion chromatography based on  
15 the difference in size and shape of the proteins to be eluted was used. The fraction corresponding to the 200 mM NaCl elution is deposited on the column. During the elution, the proteins of low molecular mass are retained and therefore eluted later than the large  
20 molecules. The purifications were carried out on HPLC with a TosohHaas TSK Prep G 3000 SW column having a diameter of 21.5 mm and a length of 300 mm, the molecular mass exclusion limit is 500 000 daltons. The elution buffer used contains 100 mM phosphate, 100 mM  
25 sodium sulfate, at pH 6.8. The separation of the protein mixture was carried out in 60 min. Only the fraction corresponding to a mass of 15-20 000 daltons was preserved. This fraction is dialyzed in 20 mM Tris buffer containing 0.2 mM  $\text{CaCl}_2$ , pH 7.2, and then  
30 freeze-dried.

At each stage, only the fractions having a significant toxic activity were retained for the next stage. The toxic activity of the proteins was checked at each  
35 stage using the MTT test. Only the fractions having a significant toxic activity were retained for the additional purification stage described in example 3.

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Example 3: Additional purification of the urinary proteins by reverse phase chromatography

5 Pools of urine from MS patients (MS-positive pool) and from non-MS patients (MS-negative pool), obtained after purification according to example 2, were taken up in distilled water and then diluted with a 0.2% TFA/10% acetonitrile solution in order to obtain a final concentration of about 130 to 140 µg/ml.

10 The separation by C8 reverse phase HPLC was carried out on a Brownlee Aquapore column (trade name) marketed by the company Perkin Elmer (column characteristics: 300 angstroms/7 µm/(100×4.6) mm). Two separate columns  
15 were used for the positive and negative pools respectively. The injections were carried out by multiple injections of 250 µl. The proteins were eluted with a linear gradient from 5% to 15% of buffer B over 5 min, and then from 15% to 100% of buffer B over  
20 95 min, at a flow rate of 0.5 ml/min. The separation buffers A and B used are the buffer 0.1% TFA (Pierce No. 28904)/MilliQ water and the buffer 0.09% TFA/80% acetonitrile (Baker) respectively. The detection was carried out by measuring the UV absorbance at 205 and  
25 280 nm. Fractions were collected in 1.5 ml and 0.5-1 ml fractions in the zone of interest. The fractions were frozen after collection in dry ice.

30 The fractions collected were then dried in a speed vac and taken up in 100 µl of 0.1% TFA/30% acetonitrile, 20 µl of the fractions were transferred into 500 µl eppendorfs, dried and washed twice with 100 µl of MilliQ water and then dried again.

35 The toxic activity of the proteins contained in each fraction collected after elution was determined with the aid of the MTT test. Only fraction 21 exhibiting a significant toxic activity was retained. The number for this fraction corresponds to the order of elution as a

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function of the elution conditions stated in this example.

Example 4: Analysis of the proteins obtained by HPLC  
5 separation on SDS-TRICINE gel

The collection pool for fraction 21 obtained by HPLC,  
as described in example 3, and resulting from 20  
injections of the MS-positive pool, was deposited on a  
10 precast 16% SDS-TRICINE gel of 10 wells and 1 mm thick  
(marketed by the company Novex). The conditions for  
using the gel correspond to those recommended by the  
supplier. The sample is taken up in 75  $\mu$ l of 1 times  
concentrated sample buffer (SDS-TRICINE No. LC 1676,  
15 1 ml two times concentrated + 50  $\mu$ l of  $\beta$ -mercapto-  
ethanol (Pierce) diluted 1/2 in water) and 25  $\mu$ l of the  
sample are deposited on the gel in three portions. The  
collection pool for fraction 21 obtained from 6  
injections of the MS-negative pool was deposited on the  
20 gel under the same conditions as described for the MS-  
positive pool. The migration on the two gels was  
carried out in parallel in the same migration tank  
(XCELL II NOVEX (trade name)) at a constant voltage of  
125 mV for 2 hours. The tank is placed in a container  
25 containing ice. The gels were stained directly after  
migration by zinc/imidazole staining (staining kit 161-  
0440 marketed by the company BIORAD) so as to obtain a  
reversible negative staining. The protein bands are  
translucent on an opaque base.

30

Example 5: Digestion of the gel bands with trypsin

All the protein bands visualized in the deposits of  
fraction 21 were cut out and subjected to proteolysis  
35 with trypsin.

The gel bands are cut out with a scalpel into slices of  
1 mm and transferred into eppendorf tubes. The  
eppendorfs are subjected to a centrifugation peak so as

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to cause the gel pieces to fall and, after centrifugation, 100  $\mu$ l of washing buffer (100 mM  $\text{NH}_4\text{CO}_3$ /50%  $\text{CH}_3\text{CN}$ ) are added to the gel pieces. After stirring for 30 min at room temperature, the  
5 supernatant is removed in fractions of 20  $\mu$ l and the washing step is repeated twice. The eppendorfs are dried for 5 min in speed vac. 20  $\mu$ g of trypsin (modified sequenal grade PROMEGA V5111) are taken up in 200  $\mu$ l of digestion buffer (5 mM TRIS, pH 8) and are  
10 dissolved for 30 min at room temperature, with intermittent stirring, and 20 to 30  $\mu$ l of resuspended trypsin are added to the gel pieces. The eppendorfs are centrifuged and stored in a hot room at 28°C overnight. After digestion, the gel bands may be used immediately  
15 for the measurements of mass or frozen for subsequent use.

Example 6: Chemical digestion of the gel bands with CNBR

20

In the event of a protein being resistant to enzymatic cleavages, in particular to the action of trypsin as described in example 5, the bands between 16 kD and 20 kD were treated with CNBR. The gel bands, already  
25 used for the digestions with trypsin, are dried for 5 to 10 min in speed vac.

A solution of CNBR (FLUKA) at 200 mg/ml was prepared in 70% formic acid (BAKER). 20  $\mu$ l of this solution were used to rehydrate the gel pieces. The reaction was  
30 carried out for 20 h at room temperature and in the dark. The peptides are extracted for 3 times 30 min with 100  $\mu$ l of 0.1% TFA/60% acetonitrile. The extraction solutions are combined and concentrated to 20  $\mu$ l. These samples are diluted 5-fold in 0.1% TFA/  
35 water. The separation conditions are those described for the peptides from the digestion with trypsin.

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Example 7: Analysis by MALDI-TOF spectrometry

30 µl of extraction buffer (2% TFA/50% acetonitrile) are added to the samples. The eppendorfs to be analyzed  
5 are subjected to a centrifugation of 5 min, and then to a sonication of 5 min, and finally to a centrifugation of 1 min.

On a stainless steel disk, 14 deposits of 0.5 µl of matrix (α-cyano-4-hydroxytranscinnamic acid at  
10 saturation in acetone) are carried out. A fine uniform microcrystalline layer is obtained. 0.5 µl of a solution of 2% TFA/water are deposited on this sublayer on the 14 deposits, and then 0.5 µl of sample to be analyzed are added. 0.5 µl of a solution at saturation  
15 with α-cyano-4-hydroxytranscinnamic acid acid in 50% acetonitrile/water is added to this drop thus formed. After drying at room temperature for 30 min, the crystalline deposits are washed with 2 µl of water which are immediately evacuated by a puff of air. All  
20 the spectra are obtained on a BRUKER BIFLEX (trade mark) mass spectrometer equipped with a reflectron. The measurements (90 to 120 laser shots on the entire deposit) are accumulated in order to obtain a mass spectrum which is most representative of all the  
25 peptides present in the matrix-sample sandwich. For each deposit, a calibration with the peptides from the autolysis of trypsin was made in order to be able to use a measurement accuracy of less than 100 ppm.

Searches in databanks were carried out in MS-FIT  
30 PROTEINPROSPECTOR (<http://prospector.ucsf.edu>). The common parameters used in these searches are (1) database: NCBI nr, (2) a tolerance of 100-50 ppm, (3) the cysteins are not modified, (4) the methionines may be oxidized, (5) molecular weight range: 1 000-  
35 100 000 Da, (6) up to 3 cleavage sites may be ignored.

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Example 8: N-terminal sequencing of the digestion peptides

5 (i) Extraction and separation by HPLC of the digestion peptides.

After the measurements of mass on the entire digestion, the rest of the peptides are extracted 3 times 30 min in a sonication bath with 0.1% TFA/60% acetonitrile.  
10 The extraction solutions are combined and dried up to 20 µl in speed vac. After dilution in 80 µl of buffer A (0.1% TFA/water), the extractions of the gel bands, digested with trypsin, are injected onto a C18/MZ-Vydac/(125x1.6) mm/5 µm column. The elution of the  
15 peptides is carried out at a flow rate of 150 µl/min, in a gradient ranging from 5% of buffer B (0.09% TFA/80% acetonitrile) to 40% of buffer B over 40 min, and then from 40% of buffer B to 100% of buffer B over 10 min. The detection is made by measuring the UV  
20 absorbance at 205 nm. The collection of the peaks is carried out in 500 µl eppendorf tubes. The fractions are stored on ice and, for the band of 18-20 kD of the MS-positive pool 21, analyzed by MALDI-TOF mass spectrometry.

25

(ii) N-terminal sequencing

The fractions corresponding only to a single mass peak were analyzed by Edman degradation on a sequencer  
30 (model 477A PERKIN ELMER/Applied Biosystems). The sequencing conditions are those described by the manufacturer. A microcartridge was used for depositing the samples and the PTH-amino acids are identified with an online HPLC system (model 120A PERKIN ELMER/Applied  
35 Biosystems).

The deposition of the fraction to be sequenced is made in several depositions of 15 µl with intermediate dryings. The tube which contained the peptide is washed



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with 15 µl of 85% formic acid (BAKER). The amino acid sequences still correspond to the masses measured. The peptides, whose masses do not correspond to the principal protein identified, were sequenced as a  
5 priority. In this manner, it was possible to identify up to three proteins in a gel band.

#### Example 9: Results and discussion.

10 After reversed HPLC of the MS-negative control pool and of the MS-positive pool, the toxic activity of each elution fraction was determined using the MTT test. Only fraction 21 of the MS-positive pool exhibits a toxic activity *in vitro*. Fraction 21 of the MS-negative  
15 control pool exhibits no toxic activity. The toxic activity of fraction 21 of the MS-positive pool was confirmed *in vitro* by FACS, as described in patent application WO 98/11439 on murine astrocyte cells.

20 The protein content of fraction 21 of the MS-negative control pool and of the MS-positive pool was observed after separation on 16% SDS-TRICINE gel and staining of the gel with zinc/imidazole. Proteins of high apparent molecular weights were found in the two fractions. On  
25 the other hand, five different bands of low apparent molecular weights are only visible in fraction 21 of the MS-positive pool (bands 8, 14, 18 and 20 kD). To each band there corresponds at least one protein and variants of said proteins which have an apparent  
30 molecular weight close to that of the native protein. These variant sequences exhibit a percentage homology or identity with the native sequences of at least 70%, preferably of at least 80% and advantageously of at least 98%.

35

The proteins of interest of fraction 21 of the MS-positive pool were then analyzed by mass spectrometry and/or sequencing and searching for homology in the databanks. The results show the presence of five

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protein bands migrating between 22 and 5 kD in fraction 21 of the MS-positive pool and variants of said proteins.

5 These proteins are the C-terminal fragment of Perlecan, which starts at amino acid 3464 and ends at amino acid 3707 of the complete protein sequence, identified in the sequence identifier SEQ ID No. 2, the precursor of the retinol-binding plasma protein whose sequence is  
10 given in SEQ ID No. 4, the precursor of the ganglioside GM2 activator identified in SEQ ID No. 8, calgranulin B identified in SEQ ID No. 17 and saposin B represented in SEQ ID No. 24. As described above, homologs or variants of said proteins were also identified by  
15 sequencing. These homologous or variant protein sequences are the product of mutations in the genes encoding said proteins. By way of example, SEQ ID No. 9 exhibits 99% homology or identity with SEQ ID No. 8 of the precursor of the ganglioside GM2 activator and the  
20 fragment of SEQ ID No. 9 which starts at amino acid 34 and ends at amino acid 202 exhibits 98.88% homology or identity with the fragment corresponding to the native protein identified in SEQ ID No. 8.

25 Example 10: Identification of the proteins in a urine sample

Urine samples from an MS-negative individual and from an MS-positive patient were collected. These urine  
30 samples were purified according to the protocol described above. The final elution fractions 21 were analyzed separately by mass spectrometry. The mass profile of each fraction corresponding to each urine sample was compared with the mass profile obtained for  
35 the proteins identified in the preceding examples. The results show that for the urine sample from the MS-positive patient, the masses correspond to the molecules (i) C-terminal fragment of Perlecan, (ii) precursor of the ganglioside GM2 activator protein,

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(iii) calgranulin B and (iv) saposin B identified above. On the other hand, none of these masses was identified in the mass profile obtained after analysis of the urine sample obtained from the MS-negative individual. The method described can be used as a diagnostic assay.

#### Example 11: Western blot assay

Western blottings were carried out on different fractions of crude or purified urine as described in example 2. Urine samples from healthy individuals and from patients suffering from multiple sclerosis are tested in parallel. The samples are deposited on an electrophoresis gel which makes it possible to separate the various proteins according to their molecular mass under the action of an electric field. The Western blottings are carried out after transferring the proteins from the gel onto a membrane. To visualize the transferred proteins, the membrane is saturated with saturation buffer and then incubated with an antibody directly labeled with alkaline phosphatase. The antibody used is an anticalgranulin antibody (mouse monoclonal antibody, clone CF 145 subtype IgG 2b marketed by the company Valbiotech: reference MAS 696p batch PC96G696). The substrate for the enzyme is 3,3'-(1,1'-biphenyl)-4,4'-diazonium dichloride and sodium 2-naphthalenylphosphate (marketed under the name  $\beta$  Naphthyl acid phosphate Sigma ref. N7375 and Tetrazotized  $\delta$ -dianisine D3502) is added for revealing the bands and visualizing the proteins linked to the antibody. A molecule with an apparent molecular mass of about 14 000 is revealed in the purified urines from patients suffering from MS, with a relatively intense signal. This protein corresponds to calgranulin B (apparent molecular mass: 14 kD). By contrast, no signal is observed from urine from healthy individuals. This observation confirms the presence of this protein specifically in the urines from patients suffering from

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MS and the use of a method of detection using an antibody recognizing the protein.

#### Example 12: Production of monoclonal antibodies

5

The production of monoclonal antibodies using ascites requires compatibility of the H-2 system between the hybridoma and the producing mouse. Twenty 6-week-old female Balb/c mice receive an injection of 0.5 ml of  
10 Pristane (2,6,10,14-tetramethylpentadecane acid) in their peritoneal cavity, for the production of ascites (Porter et al., 1972). One week to 10 days later,  $5 \times 10^6$  to  $10 \times 10^6$  hybridomas, diluted in 0.5 ml of sterile buffer containing 0.145 M NaCl, 10 mM  $\text{Na}_2\text{HPO}_4$ ,  
15 2.7 mM KCl and 1.5 mM  $\text{KH}_2\text{PO}_4$  at pH 7.4, are injected by the intraperitoneal route. The ascites appear one to two weeks later. The ascitic fluids present in the peritoneal cavity are then collected with a syringe after incision of the peritoneum. The fluid collected  
20 is centrifuged at 3 000 g for 15 minutes at room temperature, filtered on gauze in order to remove the fat, and then buffered by adding 1/20th of its volume of 1M Tris-HCl at pH 8.0. This method makes it possible to obtain quantities of antibody 10 times higher than  
25 those obtained by hybridoma culture.

The immunoglobulins present in the ascitic fluid are released by the salts (ammonium sulfate or sodium sulfate). The ascitic fluid is precipitated with 40% ammonium sulfate. After 20 minutes in the cold, the  
30 solution is centrifuged for 15 minutes at 8 000 g at 4°C. The precipitate is washed and resuspended in the cold in a 40% ammonium sulfate solution and then centrifuged again. The new precipitate enriched with IgG is redissolved in PBS buffer and dialyzed overnight  
35 against the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4. In parallel, an agarose-Protein A (or protein G) column (marketed in the freeze-dried form, Pierce) is extensively washed with the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4. The solution

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enriched with IgG is deposited on the column and then the column is washed. The IgGs retained by the column are eluted at acidic pH (200 mM glycine, pH 2.8). The eluted fractions are neutralized with one volume of 1M Tris-Base, pH 10.5. The immunoglobulin content of each fraction collected is quantified by reading the absorbance at 280 nm ( $\epsilon$  1%, 1 cm = 14.0, Prahl and Porter 1968). The rich fractions are pooled. The degree of purification of the pooled IgGs is analyzed by acrylamide gel electrophoresis in the presence of SDS. The purified IgGs are dialyzed overnight against the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4, sterilely filtered, aliquoted and stored at -20°C. Their final concentration is determined by reading the absorbance at 280 nm or by micro-BCA assay. The immunogenic peptides designated by the references SEQ ID No. 58, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 58, SEQ ID No. 59, and SEQ ID No. 65 were used for the production of monoclonal antibodies, according to the protocol described above. However, it is in the capability of persons skilled in the art to define other protocols for the production of monoclonal antibodies, for example using the techniques described by Köhler and Milstein and by Galfre G. et al. previously cited or techniques derived therefrom.

Production of recombinant proteins and of polyclonal and monoclonal antibodies

Recombinant proteins:

The recombinant proteins GM2AP (SEQ ID NO. 73) and Saposin B (SEQ ID NO. 74) used to produce the calibration series for this study were produced in a prokaryotic system and purified from the clones of these two proteins obtained in our laboratory using the methods and protocols well known to persons skilled in the art.

Anti-GM2AP or anti-Saposin B antibodies:

5 The anti-GM2AP or anti-Saposin B antibodies used to carry out the study were produced in our laboratory or generously given.

10 Anti-Saposin B and anti-GM2AP polyclonal antibodies (Li et al., Glycoconjugate, 1984) were used for the study (cf the examples below): they are called SAP84 and GM2AP84.

15 Anti-GM2AP or anti-Saposin B polyclonal antibodies were produced and purified in the laboratory using the protocols and methods well known to persons skilled in the art: 50 µg of prokaryotic GM2AP or Saposin B protein purchased were injected into rabbits on days D0, D28 and D56; two booster injections were carried out once per month for two consecutive months. The two  
20 anti-GM2AP polyclonal antibodies and two anti-Saposin B polyclonal antibodies were thus obtained and their specificity toward the recombinant protein was verified by Western blotting and Elisa.

25 Anti-GM2AP or Saposin B peptides polyclonal antibodies were produced and purified in the laboratory using the protocols and methods well known to persons skilled in the art: 75 µg of GM2AP or Saposin B peptides defined, produced and coupled to KLH in our laboratory were  
30 injected on days D0, D28 and D56; several boosts were thus carried out once per month for 5 consecutive months with injection of 75 µg each time. Four anti-GM2AP peptides polyclonal antibodies, four anti-Saposin B peptides polyclonal antibodies and four anti-MRP14  
35 peptides rabbit polyclonal antibodies were obtained and their specificity toward the recombinant protein was verified by Western blotting and by Elisa. The sequence of the GM2AP, Saposin B and MRP14 peptides chosen are described in figures 1 to 3.

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The following were obtained:

- 5 - an antibody anti-mixture of two peptides of 13 and 15 amino acids of GM2AP: 189-190; an antibody anti-peptide of 18 amino acids of GM2AP: 191-192 (cf. figure 1),
- 10 - an antibody anti-mixture of two peptides of 13 and 19 amino acids of MRP14: 193; an antibody anti-peptide of 17 amino acids of MRP14: 195-196 (cf. figure 2),
- 15 - an antibody anti-mixture of three peptides of 12, 15 and 15 amino acids of Saposin B: 74-75; another antibody anti-mixture of 3 peptides of 12, 15 and 15 amino acids of Saposin B: 72-73 (cf. figure 3).

20 Anti-native fraction monoclonal antibodies were produced and purified in the laboratory using the protocols and methods well known to persons skilled in the art. The "native fraction" corresponds to the cytotoxic elution fraction obtained from the pool of 80 liters of urine from MS patients and after purification. It is the last elution fraction which  
 25 contains the three proteins GM2AP, Saposin B, MRP14. 30 µg of this purification fraction were injected into three mice on days D0, D14, D28 and the sample collection was carried out on D38. After "screening" and cell fusion, protocols known to persons skilled in  
 30 the art for establishing hybridomas and monoclonal antibodies, the hybridomas were reinjected into the mice and the ascitic fluid was recovered 10 days later. The antibodies were purified on sepharose-Protein A column and the specificity toward the fraction used for  
 35 the immunization was verified by Western blotting and by Elisa. Thus, four monoclonal antibodies were obtained: 191C1A7, 3D3F9, 18C8C5 and 7D12A8.

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Example 13: Assay of the MRP14 proteins in the urines  
by the ELISA technique

5 The MRP14, MRP8 proteins and the MRP8/14 heterocomplex  
were assayed in human urines using (i) either an Elisa  
assay technique according to the method known to  
persons skilled in the art and using the anti-MRP  
antibodies described in the preceding examples; (ii) or  
the "MRP Enzyme Immunoassay" kit marketed by BMA  
10 Biomedicals AG, Augst, Switzerland, using the  
antibodies of the kit, the protocol being carried out  
according to the leaflet in the kit.

Detection of MRP14 and MRP8/14 in urines

15

The assay was carried out using 17 urines of  
individuals from the active population (HC), 27 urines  
of patients suffering from multiple sclerosis (MS) and  
7 urines of patients suffering from other neurological  
20 diseases (OND).

- Figure 4 illustrates the levels of MRP8 assayed in  
these urines: while the MRP8 concentration is  
practically zero in the OND urines, there is no real  
25 difference in distribution between the HC and MS  
urines. It should be noted, however, that the  
differences observed are practically negligible because  
the concentrations assayed are extremely low.

30 - Figure 5 illustrates the levels of MRP14 assayed in  
the same urines: while there are no real differences in  
the distribution of the concentrations between the HC  
and OND urines, the concentrations are higher in  
certain MS urines.

35

- Figure 6 illustrates the levels of MRP8/14 hetero-  
dimer assayed in the same urines: while there is no  
real difference between the concentrations of the HC  
and OND urines, higher concentrations are observed in



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certain MS urines, perhaps corresponding to a subpopulation of MS patients characterized by an activity of the disease. MRRP8/14 assayed in the urines is a marker for the activity of the MS disease  
5 characterized by an inflammation peak).

- The recapitulative figure 7 confirms that there is no significant difference in MRP8 and MRP14 concentration between the HC, OND and MS urines, while a small  
10 difference in MRP8/14 concentration is observed between these urines, this concentration being higher on average in the MS urines and being a marker for the activity of the disease (inflammation peak).

15 Example 14: ELISA protocols used for the assay of the GM2AP and Saposin B proteins

The GM2AP or Saposin B proteins were assayed in human urines using anti-GM2AP or anti-Saposin B? polyclonal  
20 antibodies according to the Elisa protocol described by Gardas et al. (Glycoconjugate Journal 1, 37-42, 1984). The principal stages are briefly described below:

At each stage, the wells of a 96-well microplate are  
25 filled with 200 µl of the designated solution. The wells are first "coated" with a solution of GM2AP (prokaryotic recombinant protein) diluted to 50 ng/ml in a carbonate-bicarbonate buffer, pH 9.6. After incubating overnight at 4°C, the solution is removed  
30 and the wells are washed four times with PBS buffer pH 7.4 containing 0.05% Tween-20 (PBS-Tween). The microplates thus coated are stored at 4°C for about 2 weeks.

35 The urine samples at three different dilutions (20×, 40× and 80× or other appropriate dilutions) are incubated with an appropriate dilution of the anti-GM2AP or anti-Saposin B rabbit polyclonal antibody overnight at 4°C. A standard series of dilutions of a

recombinant protein ranging from 2.0 to 62.5 ng/ml is used to prepare the calibration series and are treated in the same manner. All the dilutions are made in PBS-Tween buffer containing 1 mg/ml of ovalbumin. Thus, 0.2 ml of each incubated solution is added to "coated" wells in duplicate and the plates are left for 2 hours at room temperature. The wells are then washed four times in PBS-Tween and again filled with a solution of anti-rabbit IgG goat antibodies coupled to peroxidase and diluted about 1 200-fold. After incubating for 2 hours at room temperature, the wells are washed four times in PBS-Tween and again filled with the staining reagent. The staining reagent consists of 100 mg of 2,2'-azino-di-(3-ethylbenzothiazoline)sulfonic acid and 10 µl of 30% hydrogen peroxide for one hour at room temperature and the degree of staining of each microwell is estimated by reading the absorbance at 405 nm.

20 A standard curve is constructed by placing on the x-axis the concentration of GM2AP in the calibration series or of Saposin B with a logarithmic scale and on the y-axis the percentage absorbance with a linear scale. The percentage absorbance of the sample is the  
25 absorbance ratio between the urine sample and the control which contains only the antiserum, without the soluble antigen.

A solution of recombinant protein GM2AP produced in a prokaryotic system, and having a concentration of 3 mg/ml, is diluted in 50 mM carbonate buffer, pH 9.6, and 50  $\mu$ l are added to each well of a 96-well microplate, that is 50  $\mu$ l per well of a solution at 0.5  $\mu$ g/ml. The plates thus prepared are incubated overnight at room temperature. The anti-GM2AP polyclonal antibody produced in the laboratory (rabbit 79) was purified and diluted in PBS-0.05% Tween buffer in the presence of 10% horse serum. This solution is diluted 1/8 000. The solution is used to

produce a calibration series with 8 series points covering concentrations from 0 to 500 ng/ml. A preincubation is carried out overnight at room temperature between 100 µl of antibody and 100 µl of urine sample to be assayed or of recombinant GM2AP or Saposin B protein solution serving for the calibration series. After washing the microplate in PBS-Tween, 50 µl of the incubation mixture are added per well, and then incubated for two hours at room temperature. The microplate is again washed in PBS-Tween, and then 50 µl of anti-rabbit IgG antibody coupled to peroxidase and diluted 1/5 000 are added to each microwell of the plate and incubated for two hours at room temperature. After further washings of the microplate, 100 µl of OPD are added to each well and incubated for 20 minutes at room temperature. The staining of each well, proportional to the concentration of GM2AP or of Saposin B recognized by the specific antibody used, is estimated by reading the absorbance.

A solution of recombinant protein GM2AP or Saposin B produced in a prokaryotic system, with a concentration of 3 mg/ml, is diluted in 50 mM carbonate buffer, pH 9.6, and 50 µl are added to each well of a 96-well microplate, that is 50 µl per well of a solution at 1.5 µg/ml. The plates thus prepared are incubated overnight at room temperature. The purified anti-GM2AP peptides polyclonal antibodies produced in the laboratory (rabbit 190 and rabbit 191) are used alone or as a mixture, diluted 1/1 000 for each, in PBS-0.05% Tween buffer in the presence of 10% horse serum. The calibration series is produced using the prokaryotic recombinant protein GM2AP or Saposin B diluted so as to cover the concentration range 0 to 1 500 ng/ml with 8 points. 100 µl of antibody (one antibody or the two together) are preincubated in the presence of 100 µl of urine sample to be tested or of recombinant GM2AP or Saposin B solution, overnight at room temperature. After washing the microplate in PBS-Tween, 50 µl of the

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incubation mixture are added per well and then incubated for two hours at room temperature. The microplate is again washed in PBS-Tween, and then 50 µl of anti-rabbit IgG antibody coupled to peroxidase, 5 diluted 1/5 000, are added to each microwell of the plate and incubated for two hours at room temperature. After washing the microplate, 100 µl of OPD are added to each well and incubated for 20 minutes at room temperature. The staining of each well, proportional to 10 the concentration of GM2AP or Saposin B recognized by the specific antibody used, is estimated by reading the absorbance.

Example 15: Assay of the GM2AP proteins in the urines 15

The GM2AP protein was assayed in the urines of 22 patients suffering from multiple sclerosis (MS), 5 patients suffering from other neurological diseases (OND) and 9 individuals chosen from the active 20 population and taken during a medical visit (healthy), according to the Elisa protocol described below, using anti-GM2AP polyclonal antibodies. The MS patients selected for this study are confirmed patients, that is to say with various stages and profiles of the disease, 25 and different treatments, and the like.

The results of the assay are presented in figure 8. Whereas only 0/5 OND urines and 2/9 so-called "Healthy" urines have a GM2AP concentration greater than 30 200 ng/ml, 10/22 (that is 45%) have a concentration greater than 200 ng/ml.

These results indicate that while the GM2AP protein is present in a very low concentration (<400 ng/ml) in the 35 urines of individuals from the active population, it is present in higher concentration in the urines of MS patients. However, 12 MS urines also exhibit low levels of GM2AP. Among these 12 patients, 10 are under treatment. The high urinary concentrations of GM2AP

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appear to be a marker for the MS pathology, and more precisely a marker for one stage or one form of the disease, for the activity of the disease, and is certainly influenced by any ongoing treatment. It  
5 should be noted that two individuals in the active population have high GM2AP concentrations (these two cases were voluntarily included in the study, because they both exhibited a gliotoxic activity in their urines unlike the other individuals of this same  
10 category). It is impossible to know if they are healthy individuals, or individuals suffering from a pathological condition, or individuals suffering from multiple sclerosis because the samples from the so-called "Healthy" individuals were collected  
15 anonymously, with no knowledge of their clinical file.

Higher urinary concentrations of GM2AP are detected in the urines of MS patients; a high concentration of GM2AP can then be a marker for the MS pathology, and  
20 more precisely for one form of the disease, for one stage of the disease, or for a period of activity, and may be influenced by any ongoing treatment. These high urinary concentrations of GM2AP may also have a predictive value for the onset of a worsening of the  
25 disease, or for a benign MS at the onset of a progression, and the like.

The absolute values of the GM2AP concentrations detected in the urines are dependent on the affinity  
30 and the specificity of the antibody used, but in general, the tendency between the three groups of individuals is preserved regardless of the antibody used.

35 Example 16: Assay of the Saposin B proteins in the urines

The Saposin B protein was detected in the same urine samples as those used to study the detection of GM2AP.

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The assays were carried out in parallel with those of GM2AP, in the same study, according to the Elisa protocol described below, using anti-Saposin B polyclonal antibodies.

5

The results of the Saposin B assay are presented in figure 9. 0/5 OND urines and 2/9 Healthy urines have a Saposin B concentration greater than 2 µg/ml, while 6/22 (that is 27%) exhibit a concentration greater than 2 µg/ml.

10

These results indicate that the Saposin B protein is present in each urine (so-called healthy population or so-called sick population) at significant concentrations, that is to say <2 µg/ml. These assay results are compatible with those described in the literature. However, even if Saposin B is present in each urine, it appears to be present in a higher concentration in certain MS urines. This increase in Saposin B concentration in the MS urines is perhaps masked by the basal concentration of this protein in the ordinary state. Thus, the high urinary concentrations of Saposin B appear to be a marker for the MS pathology, and more precisely a marker for one stage or one form of the disease, or for the activity of the disease, and is certainly influenced by any ongoing treatment. The Saposin B assayed alone appears, however, to be a marker which discriminates for one form or for one activity of the disease slightly less than GM2AP. It should again be noted that two individuals from the active population have high Saposin B concentrations and they are the same individuals who also had a high GM2AP concentration in their urine.

35

In conclusion, higher urinary concentrations of Saposin B are detected in the urines of MS patients; a high Saposin B concentration can therefore be a marker for the MS pathology, and more precisely for one form of the disease, for one stage of the disease, or for a

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period of activity, and may be influenced by any ongoing treatment. These high urinary GM2AP concentrations may also have a predictive value for an onset of a worsening of the disease, or for a benign MS at the beginning of a progression, and the like. However, in general, the high Saposin B concentrations alone appear to be markers which are less discriminatory than high GM2AP concentrations alone.

10 The absolute values of the Saposin B concentrations detected in the urines are dependent on the affinity and specificity of the antibody used, but in general, the tendency between the three groups of individuals is preserved regardless of the antibody used.

15

Example 17: Coassay of the GM2AP and Saposin B proteins in the urines

Figure 10 presents the GM2AP concentrations assayed in the urine samples described in figure 5 relative to the Saposin B concentration assayed in these same samples and described in figure 6. The MS samples (dark diamonds) and the OND and "Healthy" samples (white diamonds) are presented on this graph.

25

On this graph, it appears clearly that:

- the higher the GM2AP concentration in the urines, the higher the Saposin B concentration. (We have shown that it is not a general case with other proteins and that it does not indicate a renal disturbance, with the assay of creatinine in parallel for each of the samples tested);

35 - the high GM2AP and Saposin B concentrations are characteristic of the MS samples (with the exception of two urines from the active population, mentioned above). These joint high GM2AP and Saposin B concentrations are markers for the MS pathology, more

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precisely for a window of the disease (quadrant on the right and at the top of the graph).

In conclusion, this analysis confirms that high urinary concentrations of GM2AP ( $>400$  ng/ml) and of Saposin B ( $>2$   $\mu$ g/ml) are codetected in the urines of MS patients and may represent markers for the MS pathology, more precisely for one form of the disease, for one stage of the disease, or for a period of activity, and may be influenced by any ongoing treatment. It is advantageous to assay the two proteins in parallel in each sample, and to consider the two concentrations.

Assay of GM2AP and Saposin B in the urine of two patients in the form of kinetics

MS patient No. 1 - Progressive remittent form

Urines of this patient were collected during the progression of his disease. The patient was hospitalized on D0 for an attack. He was subjected on D1 to a flash of corticoids and was then monitored over time from a clinical point of view (the flash provided clinical improvement). Figure 11 shows the profile for the assay of GM2AP and of Saposin B in these urines during the progression, and figure 12 shows the profile of the product of the two GM2AP and Saposin B concentrations, indicating a codetection of high concentrations. The high GM2AP and Saposin B concentrations at the time of the attack and hospitalization decrease gradually over time after the flash of corticoids up to 90 days.

MS Patient No. 2 - Progressive form

Urines of this patient were collected during the progression of his disease. The patient was hospitalized on D0 for an attack. He was subjected on D1 to a flash of Endoxan and was then monitored over





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- to decide on an anticipated therapeutic resumption based on the clinical signs

Example 18: Correlation between the detection of the  
5 MRP14, GM2AP and Saposin B proteins in the urines and the gliotoxicity measured in these urines

To verify a correlation between the presence of these  
10 proteins alone or in combination in the urines and the gliotoxicity of the urines, the concentrations of a protein of interest and the gliotoxicity of a sample of urines from patients suffering from multiple sclerosis (MS), from patients suffering from other neurological diseases (OND) and from individuals taken from the  
15 active population termed "Healthy" were assayed in parallel. Among the MS patients, patients are noted with various forms and stages of the disease, under treatment or otherwise, at various activities of the disease.

20 The MRP, GM2AP and Saposin B proteins were assayed in human urines according to the Elisa protocols described above. The assays analyzed in this example are those described in the preceding examples. Each urine sample  
25 analyzed in Elisa was analyzed by the MTT test to measure the gliotoxicity of each sample. The gliotoxicity is expressed as a percentage of dead cells (estimated by colorimetry using tetrazolium salts) of a murine astrocyte cell line (CLTT1.1) after 48 hours of  
30 incubation in the presence of centrifuged urine.

Figure 15 represents the GM2AP concentration as a function of the gliotoxicity of the urines determined by the MTT test.

35 22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (black diamonds) were presented on the graph. They are the same urines which were studied in examples 15 and 16.

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It is observed that all the control urines (OND and Healthy) have low levels of GM2AP (<400 ng/ml) and a low gliotoxicity (<15%), with the exception of a Healthy control urine (already commented upon in  
5 example 15) for which a high GM2AP concentration and gliotoxicity are observed.

The MS urines are divided into three subpopulations:

10 - urines with low GM2AP concentration (<400 ng/ml) and low gliotoxicity (<15%),

- urines with low GM2AP concentration (<400 ng/ml) and gliotoxicity (>15%), that is essentially 3 urines,

15

- urines at high GM2AP concentration (>400 ng/ml) and high gliotoxicity (>15%).

20 These three subpopulations perhaps indicate MS subpopulations, that is to say different forms or stages of the disease, different activities of the disease, different therapeutic benefits, and the like.

25 However, it can be noted that all the urines having a high GM2AP concentration also have a high gliotoxicity.

In conclusion, a correlation is observed between high urinary GM2AP concentration and gliotoxicity (all the urines with a high GM2AP concentration are gliotoxic  
30 (10/10), and all the urines with a low GM2AP concentration are not gliotoxic (<15%), with the exception of 3 urines/12 MS). This indicates the involvement of the GM2AP protein in the mechanism of gliotoxicity, alone or in combination, in its natural  
35 or modified form, but which is recognizable by an anti-GM2AP antibody. Furthermore, the codetection of a high GM2AP concentration in the urines and of a high gliotoxicity correlates with one subpopulation of patients suffering from MS.

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Figure 16 represents the Saposin B concentration as a function of the gliotoxicity of the urines determined by the MTT test.

5

22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (light gray diamonds) were presented on the graph. They are the same urines which were studied in examples 15 and 16.

10 It is observed that the richer the urines are in Saposin B, the more gliotoxic they are. There is a fairly clear correlation between the Saposin B concentration and the gliotoxicity of the urines.

15 In conclusion: a correlation is observed between high urinary Saposin B concentration and gliotoxicity. This indicates involvement of the Saposin B protein in the mechanism of gliotoxicity, alone or in combination, in its natural or modified form, but which is recognizable  
20 by the anti-Saposin B antibody used for the assay.

Figure 17 represents the product of the GM2AP and Saposin B concentrations as a function of the gliotoxicity of the urines determined by the MTT test.

25

The 22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (light gray diamonds) of examples 15 and 16 were presented in figure 17. The gliotoxicity of these urines is analyzed  
30 according to the product of the GM2AP and Saposin B concentrations, that is to say according to the codetection of the two proteins in the urines. A correlation is very clearly observed between the product of the two GM2AP and Saposin B concentrations  
35 and the gliotoxicity which is much higher than on considering only one protein. It is observed that 5/5 of the OND urines have a low product of GM2AP and Saposin B concentration and a low gliotoxicity; 8/9 "Healthy" urines have a low product of GM2AP and

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Saposin B concentration and/or a low gliotoxicity. On the other hand, essentially three subpopulations of MS urines are distinguished:

5 - urines at low GM2AP.Saposin B concentration and low gliotoxicity (<15%),

- urines at high GM2AP.Saposin B concentration and high gliotoxicity (>15%).

10

These two subpopulations perhaps indicate MS subpopulations, that is to say different forms or stages of the disease, different activities of the disease, different therapeutic benefits and the like.

15

However, it is very important to note that all the urines having a high GM2AP and Saposin B concentration, that is to say having simultaneously a high GM2AP and Saposin B concentration, also have a high gliotoxicity. The two subpopulations of MS patients are all the more marked and clear when the three markers are considered together: gliotoxicity, high GM2AP concentration and high Saposin B concentration. This is confirmed in figure 18.

20

25

In conclusion: a correlation is observed between high urinary GM2AP and Saposin B concentration and gliotoxicity. All the urines with a high GM2AP and Saposin B concentration are gliotoxic, and all the urines with a low GM2AP and Saposin B concentration are

30

not gliotoxic (<15%), with the exception of 2 urines/22 MS. This indicates the involvement of the two proteins GM2AP and Saposin together or in combination in the mechanism of gliotoxicity, in their natural or modified form, but which is recognizable by

35

the anti-GM2AP and anti-Saposin B antibodies used for the assay. Furthermore, the codetection of a high urinary GM2AP and Saposin B concentration and of a high gliotoxicity correlates with a subpopulation of patients suffering from MS (stage, form, activity,

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monocytes and not in those of the control monocytes, on days D6 and especially D9 of the culture; the proteins are not detected beyond this kinetic. It should be noted that the antibodies used for the assay can  
5 recognize the physiological forms of the proteins, but also the complexed and/or modified forms.

It is therefore observed that the period D6-D9 during which the highest gliotoxicity is observed in the  
10 supernatant is covered by the period D3-D15 during which a less differentiated production of the negative control for GM2A is observed in the cells with quantitative and qualitative fluctuations of its cellular expression (quantity of expression and  
15 cellular localization).

Example 20: Immunohistological technique on brain sections in paraffin

20 The histological sections prepared in paraffin are made paraffin free in xylene and alcohol before undergoing a pretreatment intended to unmask the antigens; this pretreatment may correspond to (i) twice 5 minutes under microwave (750W) in the presence of a sodium  
25 citrate, citric acid buffer, (ii) a treatment with acid by incubating for 15 minutes in a 1% periodic acid solution or by incubating for 5 minutes in a 99% formic acid solution. The endogenous peroxidases are then blocked by incubating the slides for 30 minutes in 1%  
30 hydrogen peroxide, followed by extensive washing in water for 15 minutes. The background noise is blocked by incubating the slides for 30 minutes in the presence of PBS-0.03% Triton, 10% Donkey serum (for the polyclonal antibodies) or 10% Goat serum (for the  
35 monoclonal antibodies). Labeling with the primary antibody is carried out by applying 100 to 200 µl of primary antibody solution per slide (0.5 to 5 µg/ml according to the titer) in PBS-0.03% Triton and then incubating for 2 hours at room temperature. The slides

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are then rinsed 3 times in PBS-Triton for 10 minutes. Secondary antibody labeling is carried out using biotinylated antibodies capable of binding specifically to the primary antibodies, for example anti-rabbit IgG or anti-mouse IgG antibodies diluted in PBS-0.03% Triton. The slides are washed and incubated in a solution for 2 hours (2  $\mu$ l streptavidin-biotin-peroxide complex, 1 600  $\mu$ l PBS-0.03% Triton). The slides are again washed before being revealed, protected from light, in buffer A and then rinsed with water before microscope observation. Buffer A for 5 slides: 25 ml 0.05M Tris, pH 7.6, 2.5 ml 1M Imidazole, 15 ml sterile water, 2 ml DAB 5 mg/ml, 5 ml 10% ammonium nickel, 30  $\mu$ l 1% H<sub>2</sub>O<sub>2</sub>.

The same antibodies were used for an immuno-histochemical study, according to the technique briefly described below, on paraffined slides obtained by microtome section of brain collected post mortem from MS and from controls who had died from non-neurological pathologies.

The results of the analysis are summarized below:

There is no labeling of the "non-MS" and MS brains in the "normal" (non-lesioned) white substance and gray substance with the different anti-MRP8, MRP14 and GM2A antibodies. A nonspecific reactivity did not make it possible to interpret the results with the anti-saposin B antibody in this immunohistochemical application.

On the other hand, the following are noted in the plaque zones of MS brains:

- an anti-MRP14 reactivity in the macrophage and microglial cells, having a relatively homogeneous distribution over the entire stretch of the demyelination zones (plaques),

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- a lower (less frequent) anti-MRP8 reactivity essentially linked to perivascular lymphoid infiltrates

5 - a clear anti-GM2A reactivity in the macrophages and microgliocytes of the plaque zones, with a particular density in the zones constituting the "glial wall" at the peripheral limit of a plaque. Labeling of a few astrocytes was also observed in the demyelination zones.

10

These different observations show that there is a particular hyperexpression of MRP-14 and GM2A proteins in the cultures of MS monocytes producing a gliotoxic activity in their supernatant, as well as in the zones  
15 defining demyelination plaques in the MS brains. They therefore reflect the reality of the coincidence between their abnormal coexpression, the production of gliotoxic activity and the demyelination lesions.

20 Furthermore, their abnormal production in the context of MS, in macrophage blood cells as well as in those of the brain, indicates that it is justified to carry out their assay in biological fluids to correlate their quantity with the lesional and inflammatory activity of  
25 MS.

Example 21: Measurement of the activity of the T cells by proliferation of the T cells (Sredni et al., 1981).

30 The T cells are washed twice in culture medium in order to remove any trace of IL2 present in the initial culture medium. B lymphocytes (EBV-LCL) or monocytes/macrophages taken as antigen-presenting cells are irradiated at 10 000 rads, and washed twice with  
35 culture medium (RPMI).  $2 \times 10^4$  T cells ( $2 \times 10^5$  cells/ml) and  $2 \times 10^4$  irradiated autologous B cells ( $2 \times 10^5$  cells/ml) are incubated together in the presence of an increasing antigen concentration range in a final volume of 200  $\mu$ l in microwells. After 48 hours of culture at 37°C, 1  $\mu$ Ci



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of 3H-thymidine in 50 µl of RPMI medium is added to each well. The T cells, the only cells which divide, incorporate the tritiated thymidine into the DNA. After 18 hours of culture, the cells of each microwell are  
5 harvested on glass wool pastilles by aspiration. After osmotic lysis of the cells, the radioactivity incorporated into the DNA is absorbed onto the pastilles (cell Harvester 530, Inotech). Each dried  
10 pastille is placed in a plastic tube which contains 2 ml of scintillant; the radioactivity adsorbed on each of the pastilles is quantified in a liquid scintillation beta counter (LKB Rackbeta 1217). The results are expressed as an arithmetic mean of  
cpm/culture ("counts per minute").

15 Example 22: Protocol for detecting the association between the peptides and the histocompatibility molecules (approach APC transformed with a peptide binding to MHC I).

20 1) Materials:

The sources of histocompatibility molecules are currently of two main types: mutant cells and purified  
25 histocompatibility molecules.

The mutant cell used is the human T2 cell which and a variant of the T1 line produced by fusion of the CEM T lymphoma and of the 721.174 B lymphoma (Salter and  
30 Cresswell Embo J 1986, 5: 943-949). This cell, which lacks peptide transporters, contains heavy chains of class I molecules free of peptides which will be able to accept exogenous peptides.

35 Class I histocompatibility molecules purified by affinity chromatography from human B cell lines transformed with EBV can also be used. In this case, the endogenous peptides should be removed by a treatment with 1.5 M urea and 12.5 mM sodium hydroxide

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(pH 11.7) for 1 hour at 4°C, followed by their removal by a desalting column (PDLO, Pharmacia). The histocompatibility molecules are immediately placed in contact with the peptides to be tested in a PBS buffer  
5 with 0.05% Tween 20, 2 mM EDTA, 0.1% NP40 and 6 mM CHAPS, in the presence of 2 µg/ml B2m to facilitate reassociation (Gnjatic et al., Eur J Immunol 1995 25: 1638-1642).

10 The peptides tested have in general 8 to 10 residues, sometimes 11 or 12. They were synthesized by Néosystems (Strasbourg), or by Chiron mimotopes (Victoria, Australia). They are used at concentrations varying from 100 µM to 0.1 nM.

15

2) Protocol for assembly (Connan et al., Eur J Immunol 1994, 24: 777; Couillin et al. Eur J Immunol 1995, 25: 728-732).

20 Aliquots of 8.105 cells in a volume of 64 µl, distributed in Eppendorf microfuge tubes, are brought into contact with a lysis buffer containing 10 mM PBS, pH 7.5, 1% NP40, protease inhibitors (1 mM PMSF, 100 µM iodoacetamide, 2 µg/ml aprotinin, 10 µM leupeptin,  
25 10 µM pepstatin and 10 µg/ml trypsin inhibitor). The lysis is performed in the presence of the peptides to be tested for 30 minutes or 1 hour at 37°C. After removing the nonsolubilized material by centrifugation at 15 000 revolutions/minute at 4°C, the supernatant  
30 and supplemented with 140 µl of PBS containing 0.05% Tween 20, 3 mM of sodium azide, 1 mM PMSF and 10 mg/ml of bovine albumin. Each sample is incubated for 20 hours at 4°C in 2 wells of a microtiter plate of the Nunc type, Maxisorb, previously coated with a  
35 monoclonal antibody (10 µg/ml in PBS) which recognizes the histocompatibility molecules having conforming conformation(s) for the presentation of peptides and similar to that (those) present at the surface of the cells. The antibody-coated plate is saturated

beforehand with bovine albumin at 10 mg/ml in PBS-Tween before placing the sample. The second antibody which allows the detection of the assembly of the histocompatibility molecules is directed against B2m. It is coupled either to biotin (NHS-LC biotin, Pierce) or to alkaline phosphatase (P-552, Sigma) and is incubated at 2 µg/ml for one hour at 37°C. In the case of the use of biotin, an incubation of 45 minutes at 20-25°C with streptavidin coupled to alkaline phosphatase (E-2636, Sigma) is carried out. The activity of alkaline phosphatase is measured using, as substrate, 4-methylumbelliferyl phosphate (M-8883, Sigma) at 100 µM in 50 mM diethanolamine, pH 9.5 with 1 mM MgCl<sub>2</sub>. The reading is carried out at 340/460 nm with the aid of a cytofluorimeter.

### 3) Stability of the HLA/peptide complexes:

The stability of the abovementioned complexes was studied because it determines the good presentation of the antigen and the induction of the T response. To this effect, either purified HLA or the T2 cell lysate was used. With purified HLA, the endogenous peptides were removed (as described in 2)) and then it was brought into contact with the peptide to be tested in an Eppendorf tube at 37°C, for periods varying from a few minutes to several days. The following incubation phase on a 96-well plate (as described in 2) with the anti-HLA antibody is performed for one hour at 37°C. The revealing is carried out in a conventional manner. With the T2 cell lysate, all the incubations are also carried out at 37°C, after addition of all the protease inhibitors.

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JC13 Rec'd PCT/PTO 15 JAN 2002

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# CLAIMS

1. The use of at least one polypeptide comprising at least one fragment of a protein to obtain a  
5 diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing or treating a pathological condition associated with multiple sclerosis, said protein being chosen from proteins whose peptide sequence in the native  
10 state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID  
15 No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70%  
20 identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said  
25 sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.  
30
2. The use as claimed in claim 1, of at least two polypeptides in combination as defined in claim 1.
3. Use according to claim 1, characterized in that  
35 said protein is chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24 and the peptide sequences which exhibit at least 70% identity,

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preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.

4. The use as claimed in claim 3, of five polypeptides in combination, as defined in claim 3.
5. The use as claimed in any one of claims 1 to 4, characterized in that the peptide sequence of said polypeptide comprises a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.
6. The use as claimed in any one of claims 1 to 4, characterized in that the peptide sequence of said polypeptide consists of a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.
7. The use of a polypeptide fragment defined in claim 1 or in claim 3 for the preparation of an immunogenic peptide, characterized in that said peptide comprises all or part of at least one of the sequences designated by the references SEQ ID No. 58 to 65.
8. The use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein as defined in claim 1.

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9. The use as claimed in claim 8, characterized in that said nucleotide fragment encodes said protein.
- 5 10. The use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said fragment is a  
10 fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID  
15 No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID  
20 No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 67, SEQ ID No. 66, SEQ ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.
- 25 11. The use of a ligand specific for a polypeptide or for a nucleotide fragment as claimed in any one of the preceding claims to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating,  
30 preventing or treating a pathological condition associated with multiple sclerosis.
12. A method for detecting at least one protein associated with multiple sclerosis, in a  
35 biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for at least one polypeptide as defined in claim 1, and then the

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formation of a complex between said polypeptide and said ligand is detected.

- 5 13. The method as claimed in claim 12, characterized in that said ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
- 10 14. A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 1, and  
15 then the formation of a complex between said polypeptide and said ligand is detected.
- 20 15. The method as claimed in claim 14, characterized in that the ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
- 25 16. The method as claimed in any one of claims 12 to 15, characterized in that the sequence of said polypeptide comprises a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29.
- 30 17. The method as claimed in any one of claims 12 to 15, characterized in that the sequence of said polypeptide consists of a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29.
- 35 18. The method as claimed in any one of claims 12 to 15, characterized in that the biological sample is urine, cerebrospinal fluid or serum.

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19. A polypeptide, characterized in that it comprises at least one fragment of a protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment comprising at least one mutation in relation to the reference sequence SEQ ID No. 8.  
5
20. The polypeptide as claimed in claim 19, characterized in that it comprises at least two mutations in relation to the reference sequence SEQ ID No. 8.  
10
21. The polypeptide as claimed in claim 20, characterized in that it is chosen from the polypeptides which comprise the sequence SEQ ID No. 68 and the sequence SEQ ID No. 72.  
15
22. The polypeptide as claimed in one of claims 19 to 21, characterized in that it comprises a protein whose peptide sequence corresponds to SEQ ID No. 9.  
20
23. The polypeptide as claimed in one of claims 19 to 21, characterized in that it consists of a protein whose peptide sequence corresponds to SEQ ID No. 9.  
25
24. The use of at least one polypeptide as claimed in any one of claims 19 to 23 to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis.  
30
25. The use as claimed in claim 24, characterized in that said polypeptide is used in the form of a mixture with at least one polypeptide as defined in any one of claims 1 to 6.  
35



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26. A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in any one of claims 19 to 23, and then the formation of a complex between said polypeptide and the ligand is detected.
27. The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide as defined in any one of claims 1 to 5.
28. The method as claimed in claim 26 or 27, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. A method for detecting at least one polypeptide as defined in any one of claims 19 to 23, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
30. The method as claimed in claim 29, characterized in that said ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
31. The method as claimed in claim 27 or 28, characterized in that the biological sample is brought into contact with a ligand as defined in either of claims 28 and 30 and at least one ligand specific for at least one polypeptide as defined

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in any one of claims 1 to 5, and then the formation of complexes between said polypeptides and said ligands specific for said polypeptides is detected.

5

32. The method as claimed in claim 31, characterized in that the ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.

10

33. A nucleotide fragment, characterized in that it encodes a polypeptide as defined in any one of claims 19 to 23.

15

34. The use of a nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said nucleotide fragment is the nucleotide fragment defined in claim 33, optionally in combination with at least one nucleotide fragment as defined in any one of claims 8 to 10, and the fragments complementary to said fragments.

20

25

35. The method as claimed in any one of claims 26 to 32, characterized in that the biological sample is urine, cerebrospinal fluid or serum.

30

36. The method as claimed in any one of claims 26 to 32, characterized in that the degenerative and/or autoimmune disease is multiple sclerosis.

35

37. A method for detecting, in a sample of biological fluid, at least one polypeptide as defined in any one of claims 1 to 5 or in any one of claims 19 to 23, according to which, optionally after

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purification of said sample, the mass profile obtained from said sample is analyzed by mass spectrometry and compared with a reference mass profile.

5

38. The use of at least one polypeptide as defined in claim 1 to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing, or treating a pathological condition associated with multiple sclerosis, and preferably of at least one polypeptide as defined in claim 5.

10

39. The use as claimed in claim 38, in which the peptide sequences comprise the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from the precursor of the ganglioside GM2 activator and saposin B.

15

20

40. The use as claimed in either of claims 38 or 39, which is associated with the use of a detection of a gliotoxic activity.

25

41. A method for detecting, in a sample, a value for the concentration of at least one polypeptide as claimed in any one of claims 38 to 40, said concentration being associated with a pathological condition, characterized in that said polypeptide is assayed, the assay making it possible to obtain a concentration value which is compared with a threshold value representative of multiple sclerosis.

30

42. The method as claimed in claim 41, in which the threshold value is obtained by an ELISA test for a urine sample, this value being:

35

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- 400 ng/ml for the precursor of the ganglioside GM2 activator, for the GM2AP84 antibody, and
- 2 µg/ml for saposin B, for the SAPB84 antibody.

5

43. The method as claimed in claim 12, characterized in that the biological sample consists of cells or supernatants of said cells from a patient likely to suffer from multiple sclerosis.

10

44. The method as claimed in claim 43, in which the biological sample consists of monocyte or macrophage cells or of supernatants of these cells.

15

45. The method as claimed in either of claims 43 and 44, in which the biological sample consists of cells in culture or of supernatants of these cells in culture, after a period of between 6 and 12 days of culture, preferably after 9 days.

20

46. The method as claimed in either of claims 43 and 44, in which the biological sample consists of cells, ex vivo, preferably monocytes or macrophages.

25

47. The use of at least one polypeptide as defined in claim 1 for testing the efficacy of a therapeutic agent.

30

48. The use of at least one polypeptide comprising at least one fragment of a protein for the preparation of a pharmaceutical composition for treating multiple sclerosis, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID

35

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No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID  
No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID  
No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID  
No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID  
5 No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No.  
27, SEQ ID No. 28 and SEQ ID No. 29 and the  
peptide sequences which exhibit at least 70%  
identity, preferably at least 80% identity and  
advantageously at least 98% identity with any one  
10 of the peptide sequences SEQ ID No. 1 to 29, and  
the peptide sequences or the fragments of said  
sequences belonging to the same family of proteins  
chosen from Perlecan, the precursor of the  
retinol-binding plasma protein, precursor of the  
15 ganglioside GM2 activator, calgranulin and  
saposin.

49. The use as claimed in claim 47 or 48,  
characterized in that the polypeptide is chosen  
20 from SEQ ID No. 2, 4, 8, 9, 17, 24.

50. The use of at least one nucleotide fragment, to  
test the efficacy of a therapeutic agent for a  
pathological condition associated with multiple  
25 sclerosis, according to which said nucleotide  
fragment is chosen from the fragments which encode  
at least one fragment of a protein, said protein  
being chosen from proteins whose peptide sequence  
in the native state corresponds to SEQ ID No. 1,  
30 SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID  
No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8,  
SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID  
No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No.  
15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18,  
35 SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ  
ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID  
No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No.  
28 and SEQ ID No. 29 and the peptide sequences  
which exhibit at least 70% identity, preferably at

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least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the fragments complementary to said fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

51. The use, to test the efficacy of a therapeutic agent for a pathological condition associated with multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in claim 50.

52. The use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating multiple sclerosis, according to which said nucleotide fragment is chosen from the fragments which encode at least one fragment of a protein, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the fragments complementary to said fragments and the fragments which encode the peptide sequences or

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the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

53. The use, for the preparation of a pharmaceutical composition for treating multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in claim 52.

54. The use as claimed in claim 50 or 52, characterized in that said nucleotide fragment encodes said protein.

55. The use as claimed in claim 54, characterized in that the polypeptides are chosen from SEQ ID No. 2, 4, 8, 9, 17, 24.

56. The use as claimed in claim 50, characterized in that said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.

57. The use as claimed in claim 52, characterized in that said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID

No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.

58. The use as claimed in claim 56 or 57, characterized in that the nucleic sequence is chosen from SEQ ID No. 30, 31, 42, 53.

15 59. The use of lycorine for the preparation of a composition for preventing and/or treating multiple sclerosis.



## ABSTRACT OF DISCLOSURE

The invention concerns the use of at least one polypeptide comprising a protein fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing or treating a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, said protein being selected among the proteins whereof the peptide sequence in native state corresponds to SEQ ID No 1, SEQ ID No 2, SEQ ID No 3, SEQ ID No 4, SEQ ID No 5, SEQ ID No 6, SEQ ID No 7, SEQ ID No 8, SEQ ID No 9, SEQ ID No 10, SEQ ID No 11, SEQ ID No 12, SEQ ID No 13, SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17, SEQ ID No 18, SEQ ID No 19, SEQ ID No 20, SEQ ID No 21, SEQ ID No 22, SEQ ID No 23, SEQ ID No 24, SEQ ID No 25, SEQ ID No 26, SEQ ID No 27, SEQ ID No 28, and SEQ ID No 29, and the peptide sequences having at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No 1 to SEQ ID No 8 and SEQ ID No 10 to SEQ ID No 29, and the peptide sequences or fragments of said sequences belonging to a common family of proteins selected among perlecan, the precursor of the retinol-binding plasmatic protein, of the precursor of the activator of GM2 ganglioside, of calgranulin B and of saponin B.

## Rabbits anti GM2

➤ **Ganglioside GM2 activator**

2 peptides of 13, 15 amino acids rabbits 189 190

**1 peptide of 18 amino acids**

**MQSLMQAPLL IALGLLLATP AQAHLKKPSQ**

**LSSFSWDNCD EGKDPVIRS LTLEDPPIW**

PGNVTLSWVG STSVPLSSPL KVDLVLEKEV

AGLWIKIPCT DYIGSCTFEH FCDVLDMLIP

**TGEP CPEPLR TYGLPCHCPF KEGTYSLPKS**

EFVWPDLEP SWLTTGNYRI ESVLSSGKR

**LGCIAASL·KGI**

**GM2A**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 104

FIG. 1

## Rabbits anti MRP14

	2 peptides of 13, 19 amino acids	rabbit 193
	1 peptide of 17 amino acids	rabbit 195-196

MTCKMSQLER NIETINTFH QYSVKLGHPD  
TLNQGEFKEL VRKDLQNFLK KENKNEKVE  
HIMEDDLDTN ADKQLSFEF IMLMARL TWA  
SHEKMHEGDE GPGHHHKPGL GEGTP

**MRP1**

[illegible]

**FIG 2**

# Rabbit anti Saposine

3 peptides of 12, 15, 15 amino acids rabbit 74-75  
 3 peptides of 12, 15, 15 amino acids rabbit 72-73

GDVCQDCIQM VTDIQTAVRT NSTFVQALVE  
 HVKEECDRLG PGMADICKNY ISQYSEIAIQ  
 MMMHMQDQQP KEICALVGFC DEV

Sap

ATG GGG GAC GTT TGC CAG GAC TGC ATT CAG ATG GTG ACT GAC ATC CAG ACT GCT GTA CCG ACC AAC TCC ACC TTT GTC CAG  
 GCG  
 M G D V C Q D C I Q M V T D I Q T A V R T K S T F V Q  
 A  
 TTT GTG GAA CAT GTC AAG GAG TGT GAC CCG CCG GTG GGC CCT GGC ATG GCT GAC ATA TGC AAG AAC TAT ATC ACC CAG TAT  
 TGT  
 L V E H V K E E C D R L G P G M A D I C K N Y I S Q Y  
 S  
 GAA ATT GCT ATC CAG ATG ATG CAG ATG CAA CCC AAG GAG ATC TGT GCG CTT GGT GGG ATC TGT GAT CAG TCA  
 E I A I Q M M M M M Q P K E I C A L V G P C D E

FIG. 3

# MRP 8 assay

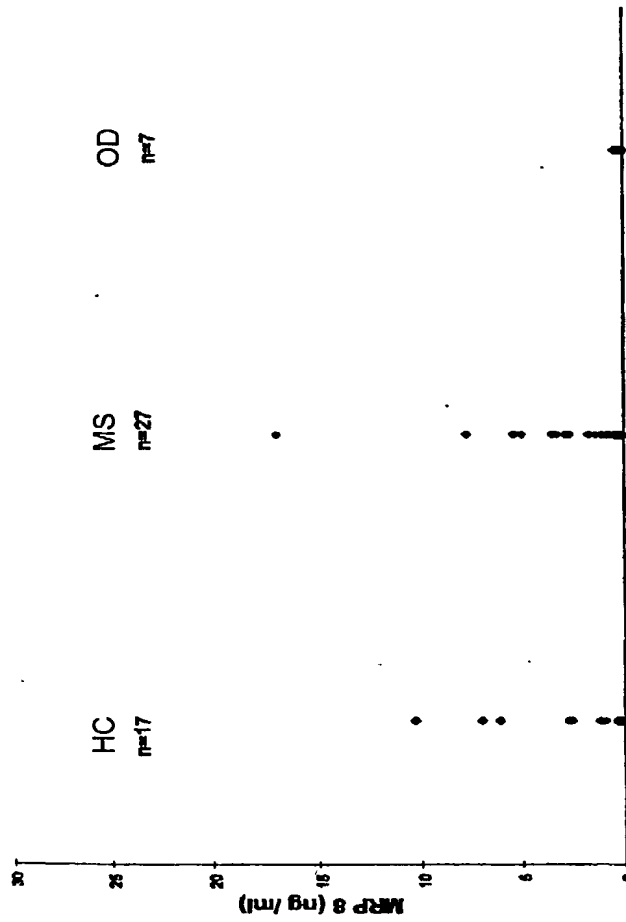


FIG. 4

# MRP14 assay

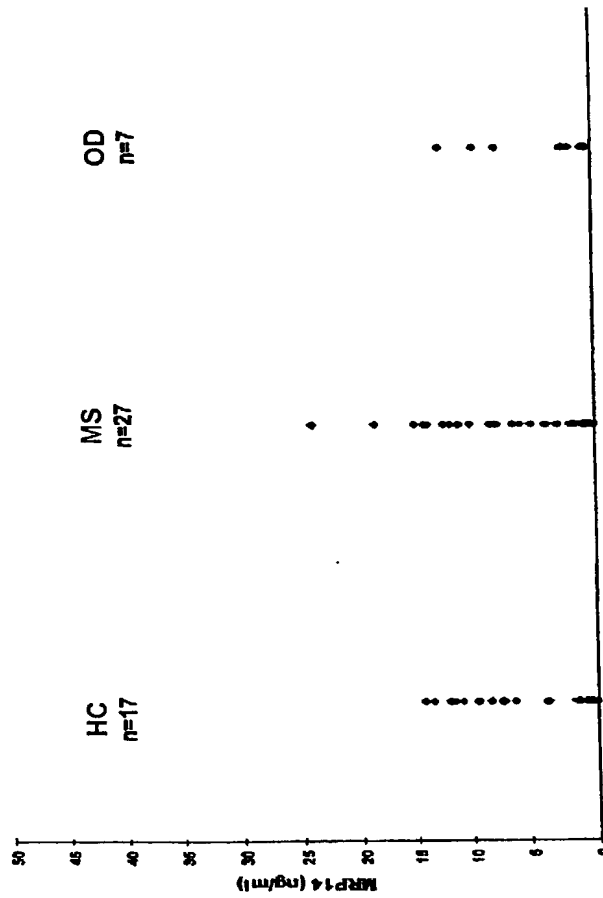


FIG. 5

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# MRP8/14 assay

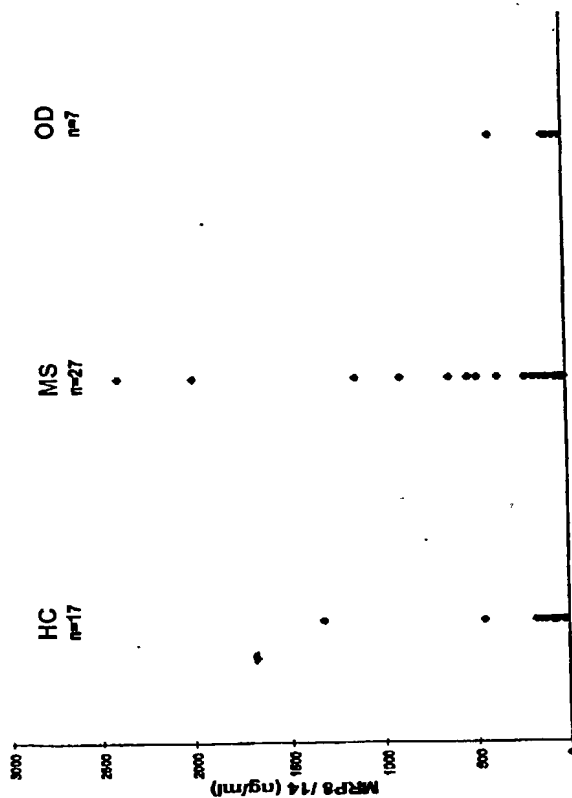


FIG. 6

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# Mean urinary level per category of population (ULC)

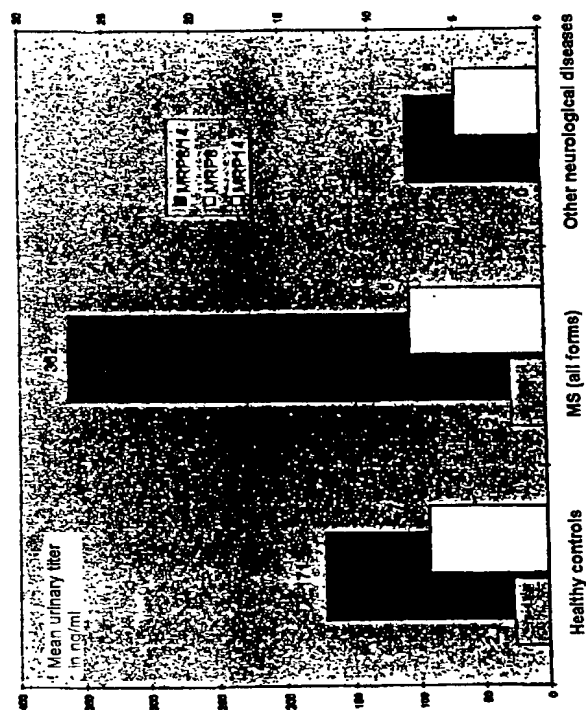
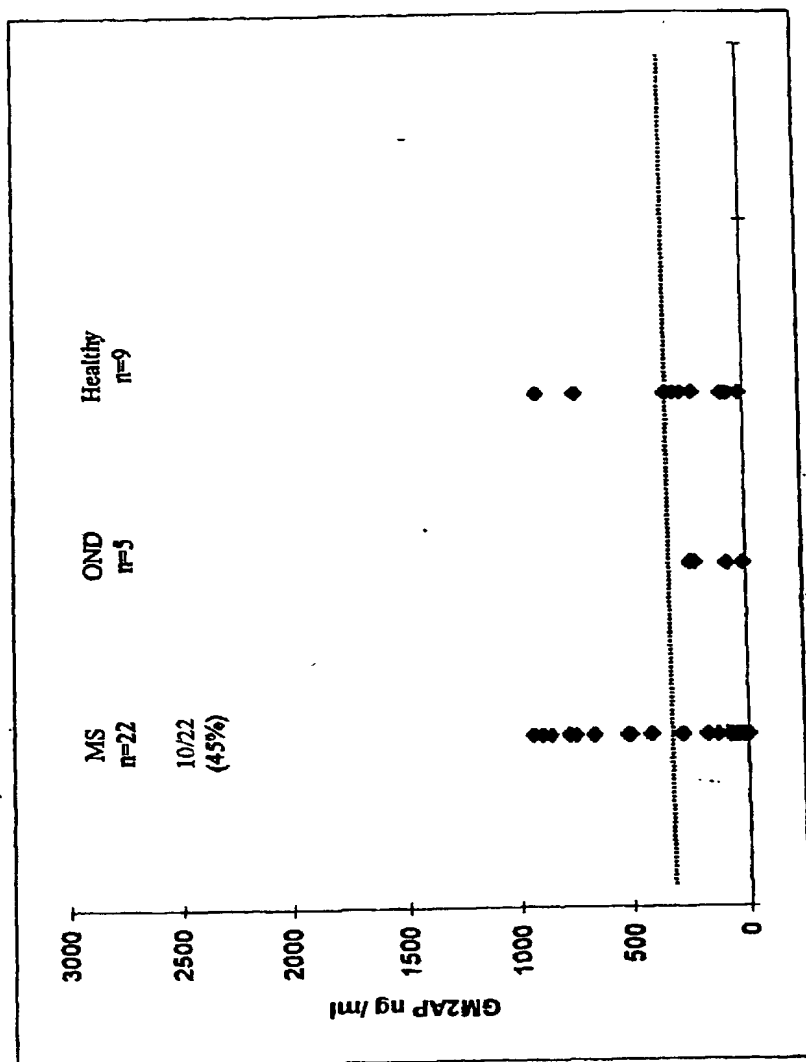


FIG. 7

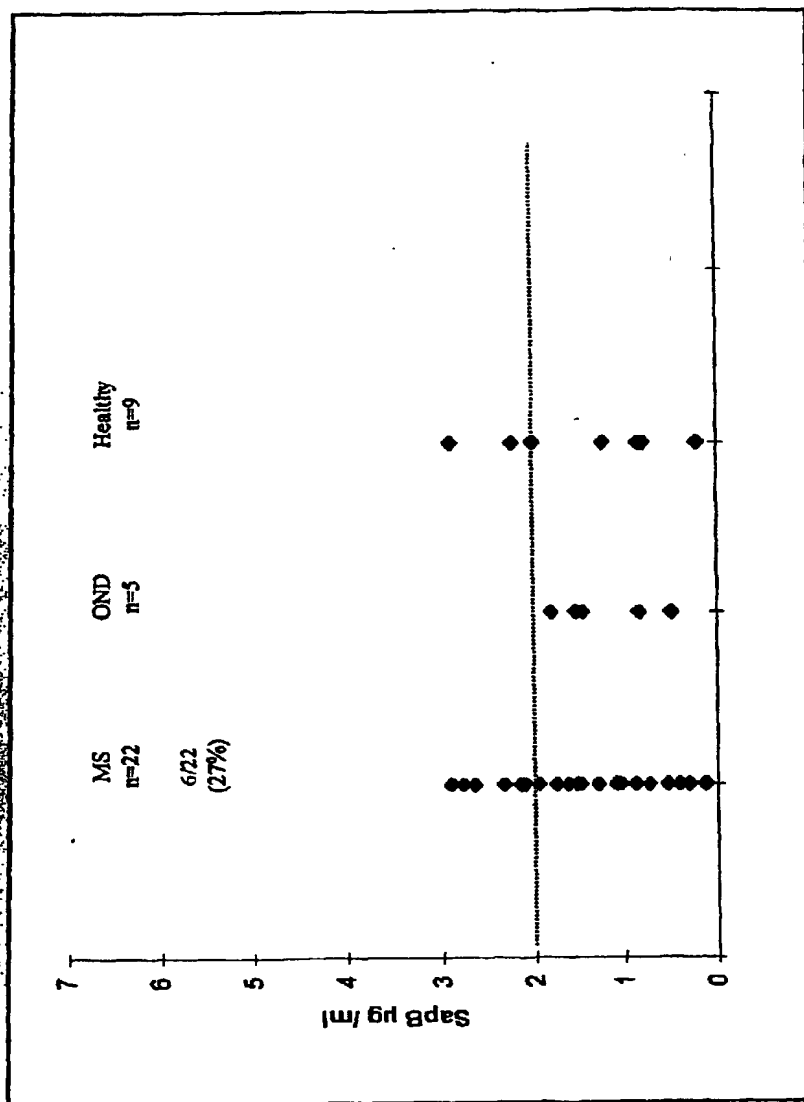


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Figure 8

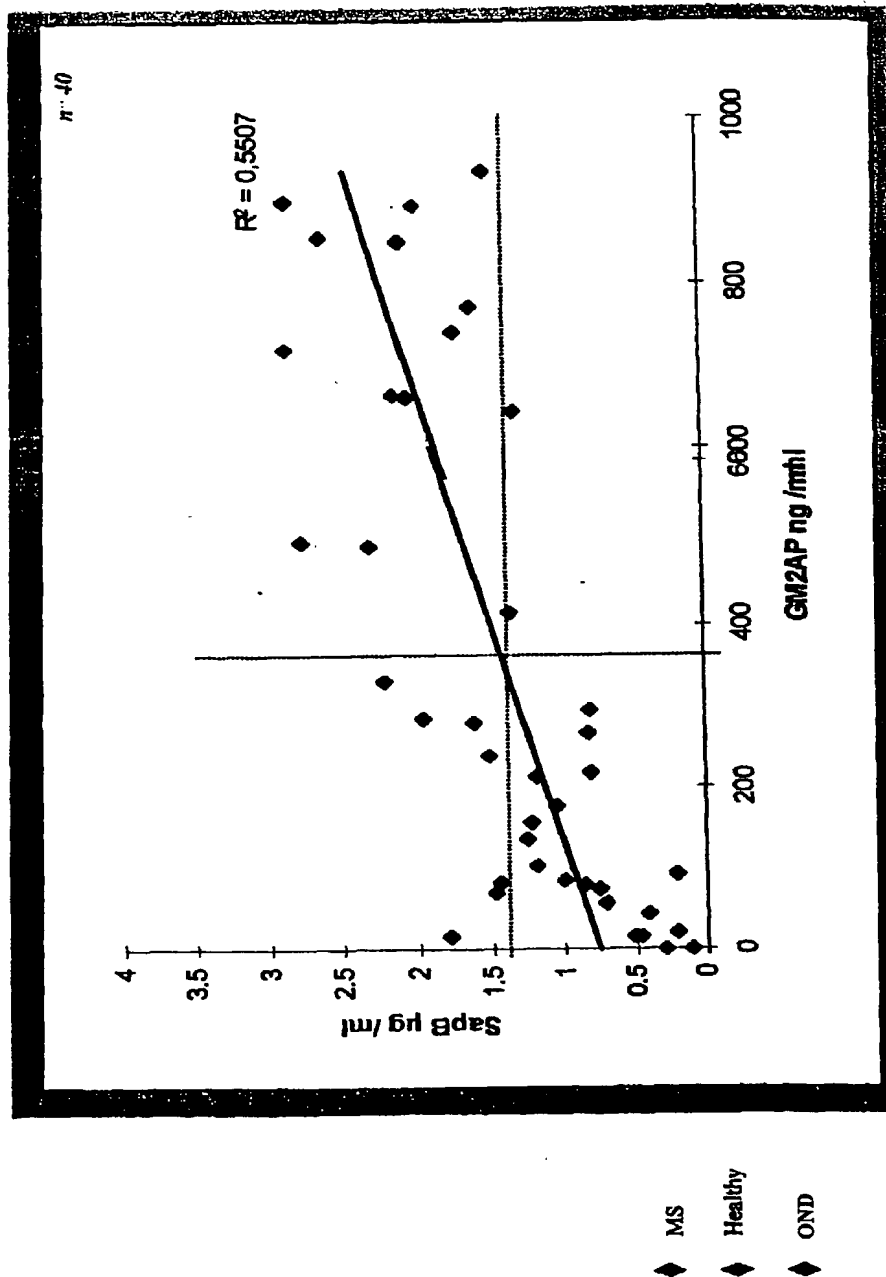


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**Figure 9**

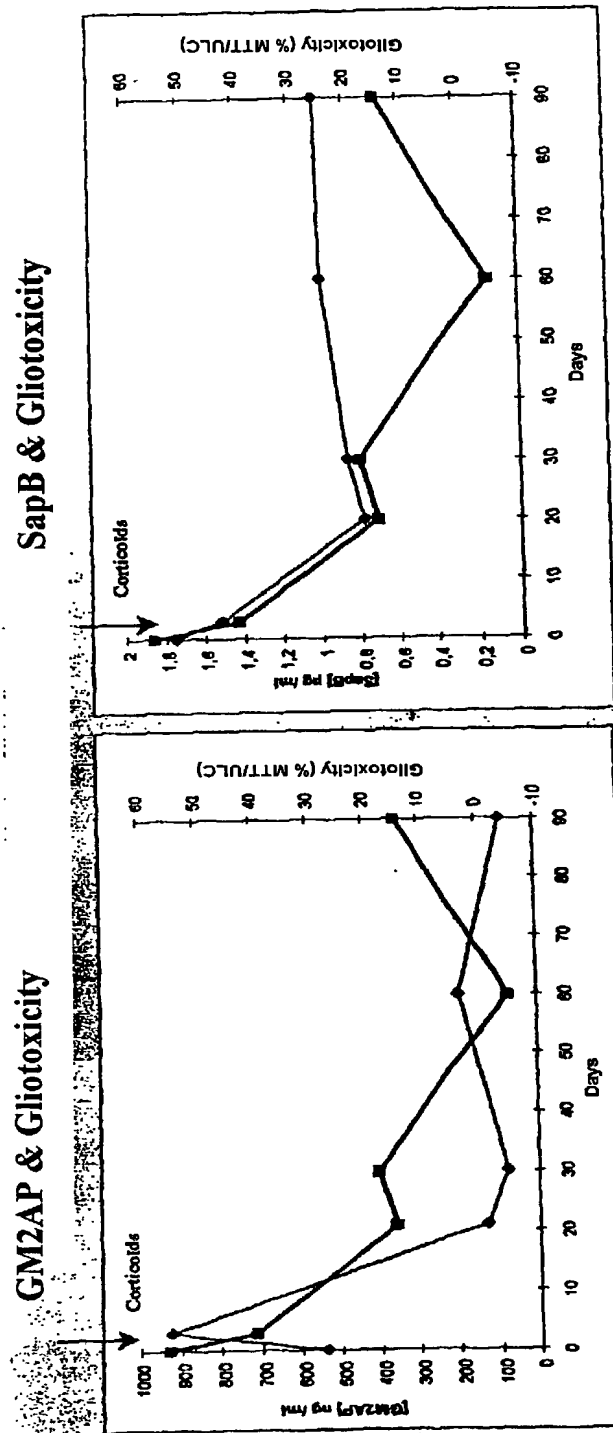
10/18

Figure 10



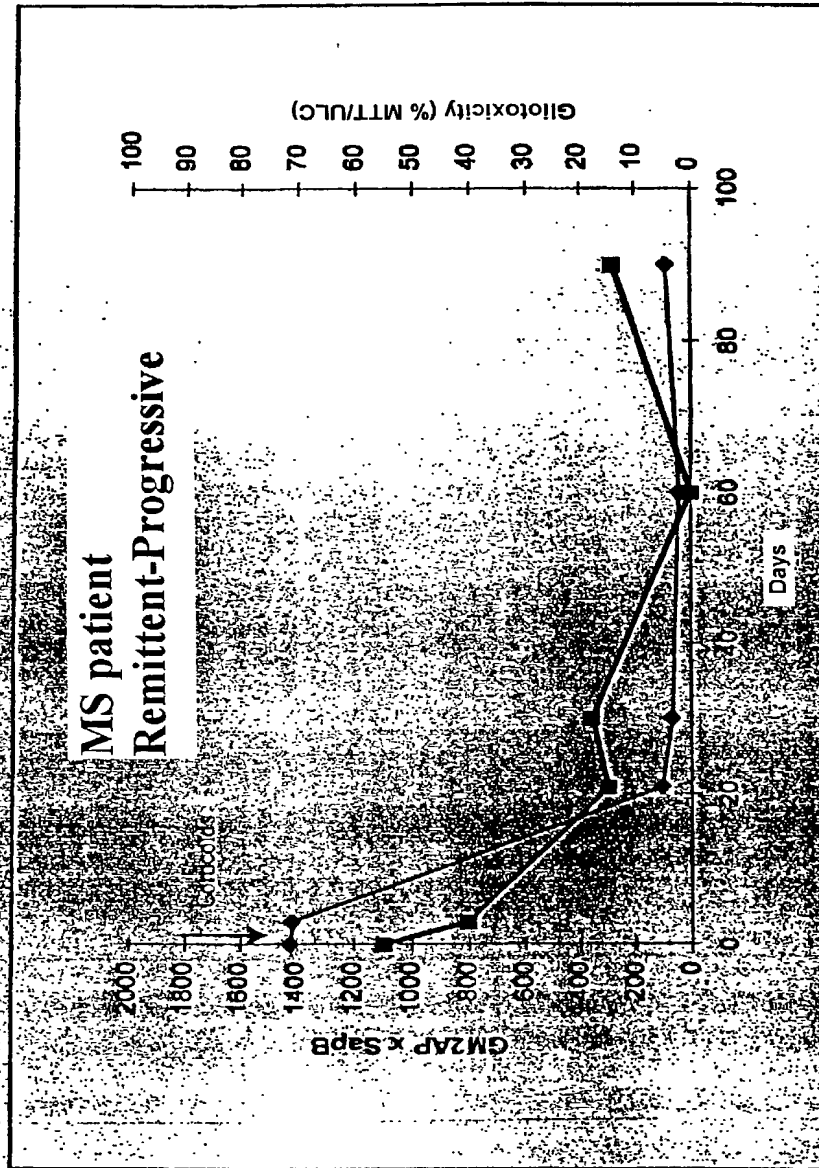
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**Figure 11**  
MS patient progressive remittent form



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Figure 12

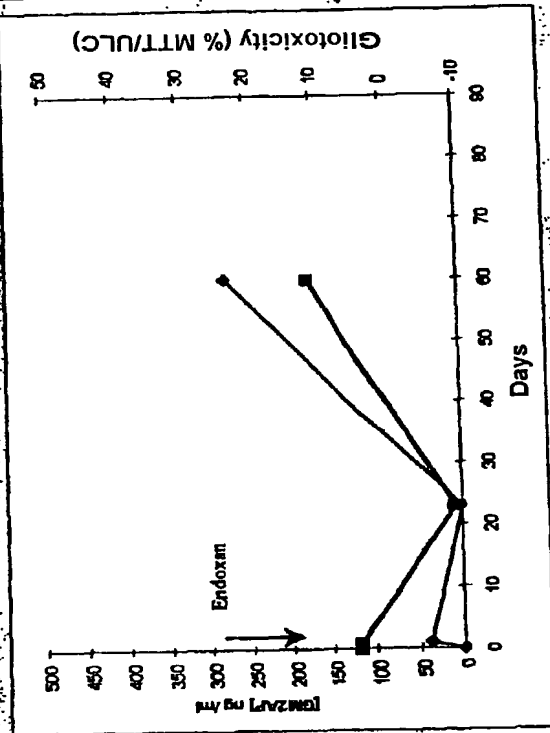


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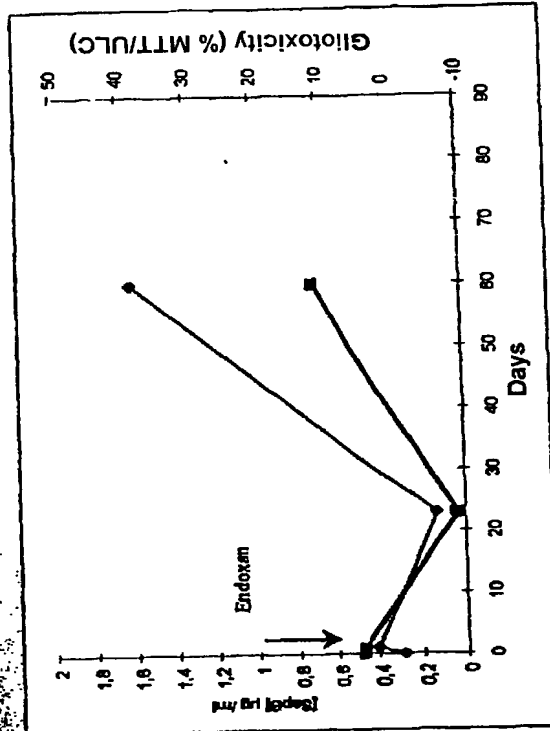
Figure 13

MS patient - Progressive

GM2AP & Gliotoxicity



SapB & Gliotoxicity



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Figure 14

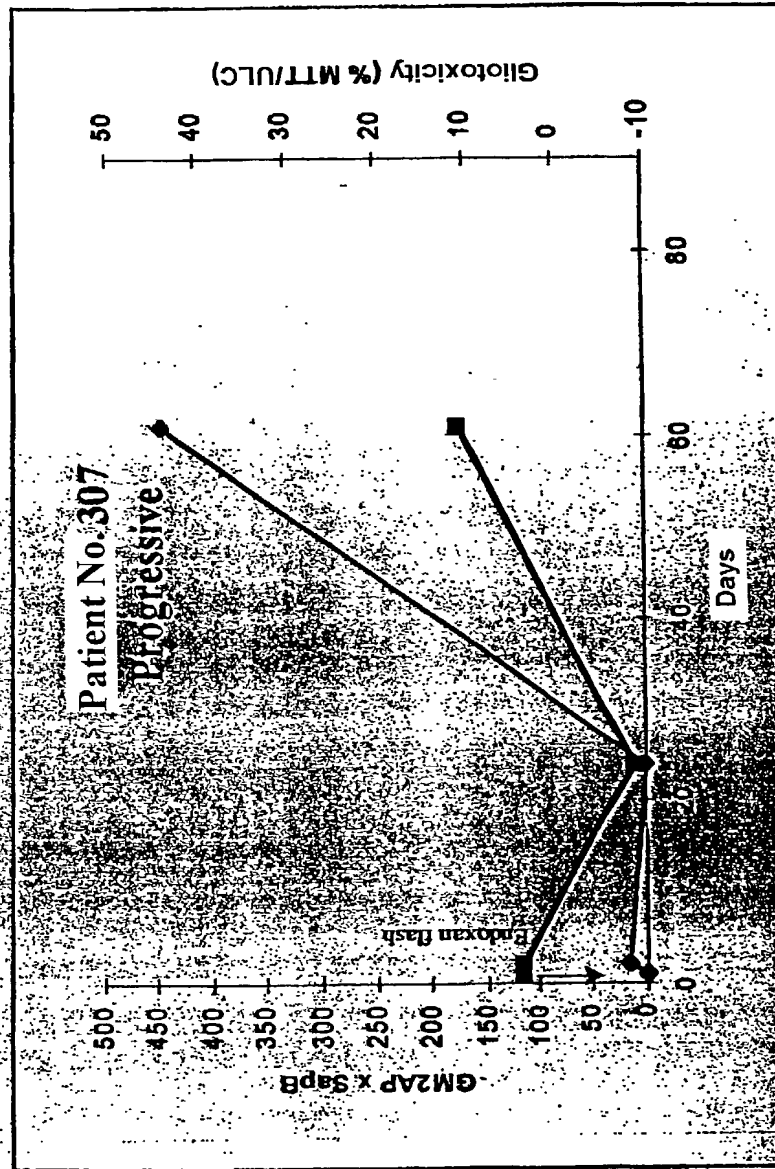


Figure 15

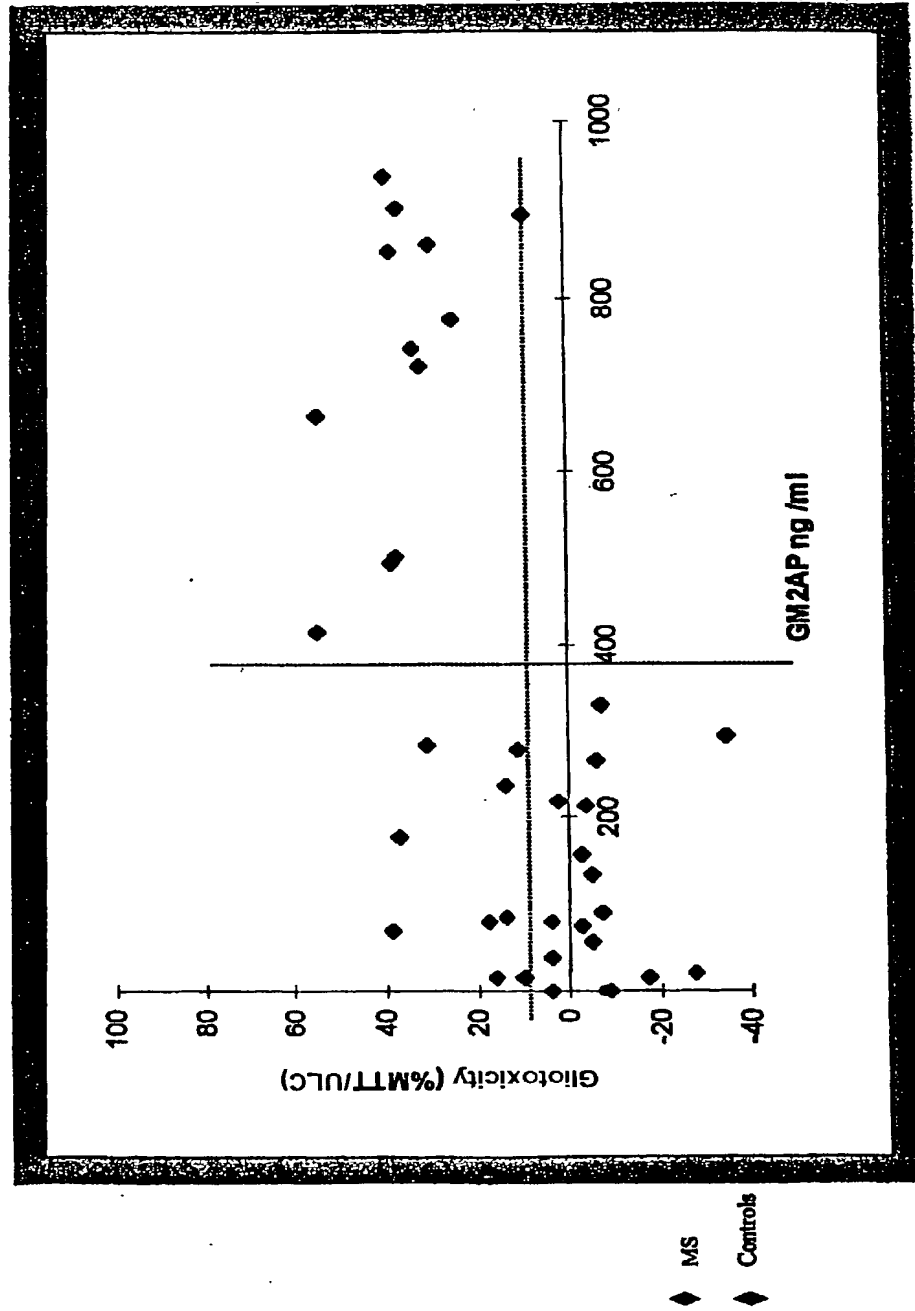




Figure 16

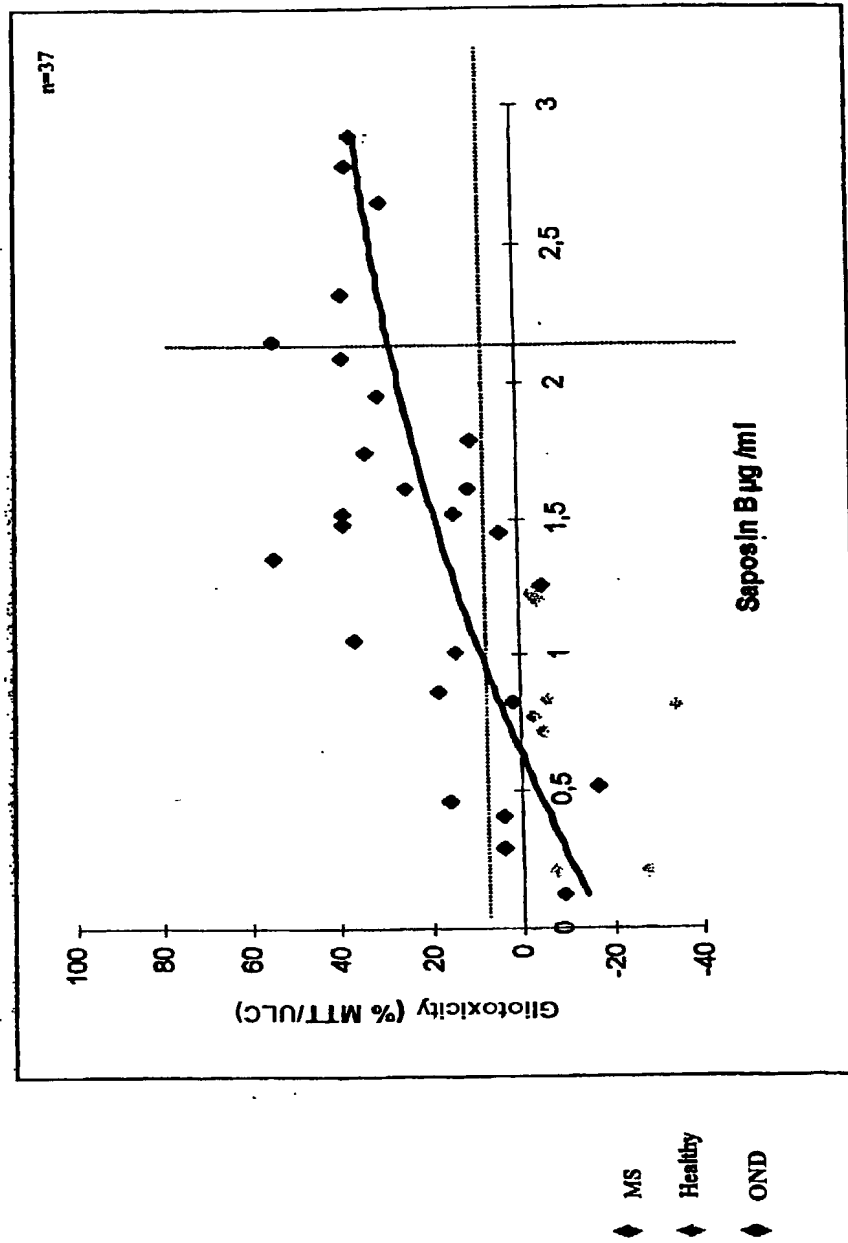


Figure 17

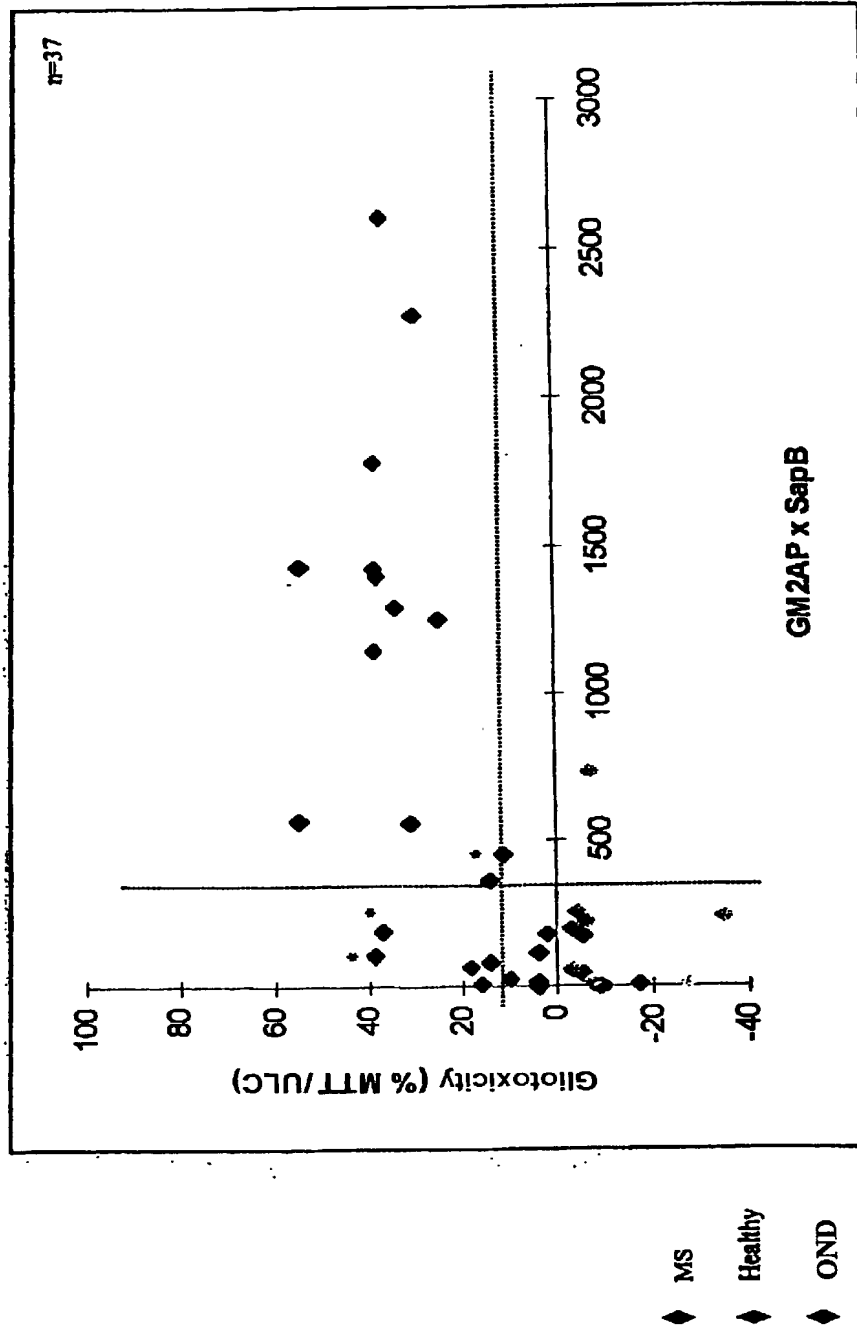
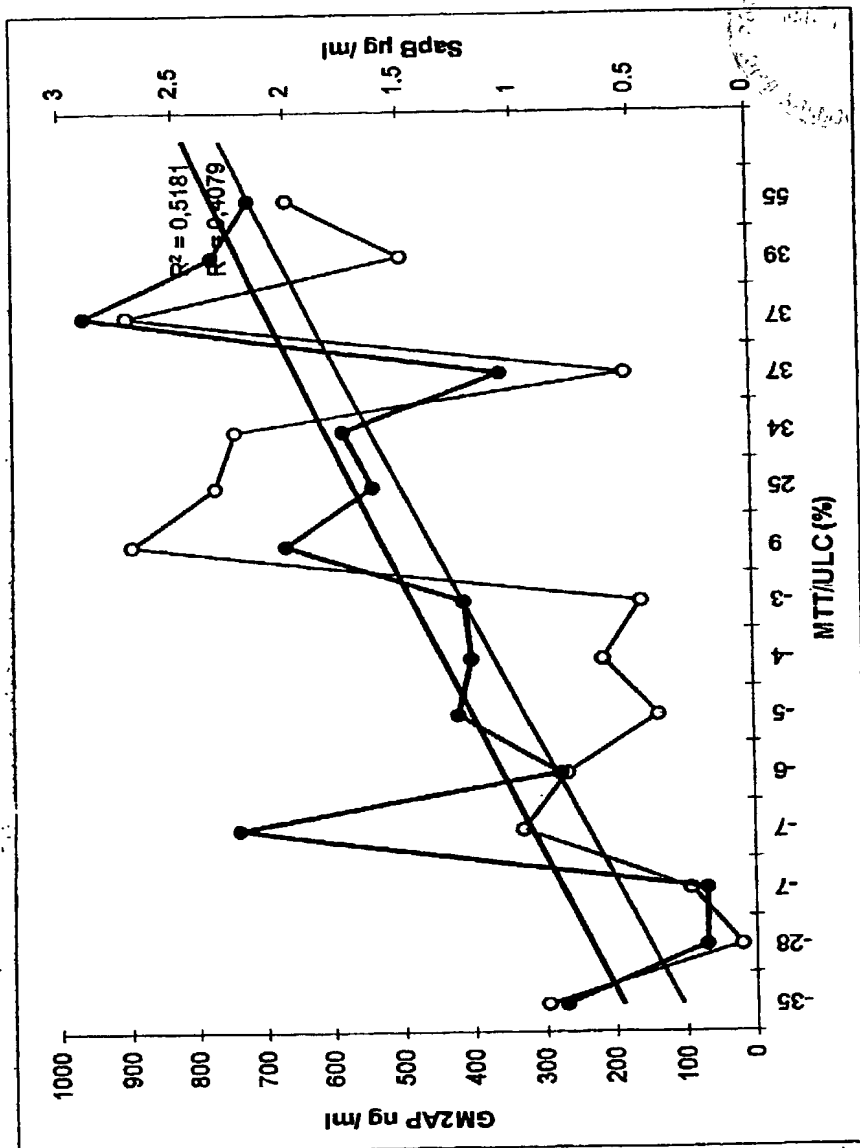


Figure 18



**DECLARATION AND POWER OF ATTORNEY  
UNDER 35 USC §371(c)(4) FOR  
PCT APPLICATION FOR UNITED STATES PATENT**

As a below named inventor, I hereby declare that:  
my residence, post office address and citizenship are as stated below under my name;

I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought, namely the invention entitled: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE

described and claimed in international application number PCT/FR00/02057 filed July 17, 2000.

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

Under Title 35, U.S. Code §119, the priority benefits of the following foreign application(s) filed by me or my legal representatives or assigns within one year prior to my international application are hereby claimed:

French Patent Application No. 99 09372 filed July 15, 1999.

The following application(s) for patent or inventor's certificate on this invention were filed in countries foreign to the United States of America either (a) more than one year prior to my international application, or (b) before the filing date of the above-named foreign priority application(s):

I hereby appoint the following as my attorneys of record with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office:

James A. Oliff, Reg. No. 27,075; William P. Berridge, Reg. No. 30,024;  
Kirk M. Hudson, Reg. No. 27,562; Thomas J. Pardini, Reg. No. 30,411;  
Edward P. Walker, Reg. No. 31,450; Robert A. Miller, Reg. No. 32,771;  
Mario A. Costantino, Reg. No. 33,565; Stephen J. Roe, Reg. No. 34,463;  
Joel S. Armstrong, Reg. No. 36,430; Christopher W. Brown, Reg. No. 38,025;  
Richard E. Rice, Reg. No. 31,560; and Paul Tsou, Reg. No. 37,956.

ALL CORRESPONDENCE IN CONNECTION WITH THIS APPLICATION SHOULD BE SENT TO OLIFF & BERRIDGE, PLC, P.O. BOX 19928, ALEXANDRIA, VIRGINIA 22320, TELEPHONE (703) 836-6400.

I hereby declare that I have reviewed and understand the contents of this Declaration, and that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1	<b>Typewritten Full Name of Sole or First Inventor</b>	<u>Dominique</u> <u>ROECKLIN</u>		
		Given Name	Middle Initial	Family Name
2	<b>Inventor's Signature:</b>	<u>Dominique Roedklin</u>		
3	<b>Date of Signature:</b>	<u>March 19 2002</u>		
		Month	Day	Year
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		City	State or Province	Country
	<b>Citizenship:</b>	<u>FRANCE</u>		
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	<b>(Insert complete mailing address, including country)</b>	<u>F-67500 Niederschaeffolsheim FRANCE</u>		

**Note to Inventor:** Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

**IF THERE IS MORE THAN ONE INVENTOR USE PAGE 2 AND PLACE AN "X" HERE** ☒

(Discard this page in a sole inventor application)

10030937 032402

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3 Date of Signature: MARCH 4th 2002  
Month Day Year  
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Month Day Year  
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This form may be executed only when attached to the first page of the Declaration and Power of Attorney of the application to which it pertains.

10/030937

## SEQUENCE LISTING

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MALCUS, Carine

SANTORO, Lyse

PERRON, Herve

<120> USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A  
 PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR  
 AUTOIMMUNE DISEASE

&lt;130&gt; 111664

&lt;140&gt; 10/030,937

&lt;141&gt; 2002-01-15

&lt;150&gt; PCT/FR00/02057

&lt;151&gt; 2000-07-17

&lt;150&gt; FR9909372

&lt;151&gt; 1999-07-15

&lt;160&gt; 75

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

&lt;211&gt; 4393

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1

Met Gly Trp Arg Ala Pro Gly Ala Leu Leu Leu Ala Leu Leu His  
 1 5 10 15

Gly Arg Leu Leu Ala Val Thr His Gly Leu Arg Ala Tyr Asp Gly Leu  
 20 25 30

Ser Leu Pro Glu Asp Ile Glu Thr Val Thr Ala Ser Gln Met Arg Trp  
 35 40 45

Thr His Ser Tyr Leu Ser Asp Asp Glu Asp Met Leu Ala Asp Ser Ile  
 50 55 60

Ser Gly Asp Asp Leu Gly Ser Gly Asp Leu Gly Ser Gly Asp Phe Gln  
 65 70 75 80

Met Val Tyr Phe Arg Ala Leu Val Asn Phe Thr Arg Ser Ile Glu Tyr  
 85 90 95

Ser Pro Gln Leu Glu Asp Ala Gly Ser Arg Glu Phe Arg Glu Val Ser  
 100 105 110

Glu Ala Val Val Asp Thr Leu Glu Ser Glu Tyr Leu Lys Ile Pro Gly  
 115 120 125  
 Asp Gln Val Val Ser Val Val Phe Ile Lys Glu Leu Asp Gly Trp Val  
 130 135 140  
 Phe Val Glu Leu Asp Val Gly Ser Glu Gly Asn Ala Asp Gly Ala Gln  
 145 150 155 160  
 Ile Gln Glu Met Leu Leu Arg Val Ile Ser Ser Gly Ser Val Ala Ser  
 165 170 175  
 Tyr Val Thr Ser Pro Gln Gly Phe Gln Phe Arg Arg Leu Gly Thr Val  
 180 185 190  
 Pro Gln Phe Pro Arg Ala Cys Thr Glu Ala Glu Phe Ala Cys His Ser  
 195 200 205  
 Tyr Asn Glu Cys Val Ala Leu Glu Tyr Arg Cys Asp Arg Arg Pro Asp  
 210 215 220  
 Cys Arg Asp Met Ser Asp Glu Leu Asn Cys Glu Glu Pro Val Leu Gly  
 225 230 235 240  
 Ile Ser Pro Thr Phe Ser Leu Leu Val Glu Thr Thr Ser Leu Pro Pro  
 245 250 255  
 Arg Pro Glu Thr Thr Ile Met Arg Gln Pro Pro Val Thr His Ala Pro  
 260 265 270  
 Gln Pro Leu Leu Pro Gly Ser Val Arg Pro Leu Pro Cys Gly Pro Gln  
 275 280 285  
 Glu Ala Ala Cys Arg Asn Gly His Cys Ile Pro Arg Asp Tyr Leu Cys  
 290 295 300  
 Asp Gly Gln Glu Asp Cys Glu Asp Gly Ser Asp Glu Leu Asp Cys Gly  
 305 310 315 320  
 Pro Pro Pro Pro Cys Glu Pro Asn Glu Phe Pro Cys Gly Asn Gly His  
 325 330 335  
 Cys Ala Leu Lys Leu Trp Arg Cys Asp Gly Asp Phe Asp Cys Glu Asp  
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 Arg Thr Asp Glu Ala Asn Cys Pro Thr Lys Arg Pro Glu Glu Val Cys  
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 Gly Pro Thr Gln Phe Arg Cys Val Ser Thr Asn Met Cys Ile Pro Ala  
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 Ser Phe His Cys Asp Glu Glu Ser Asp Cys Pro Asp Arg Ser Asp Glu  
 385 390 395 400  
 Phe Gly Cys Met Pro Pro Gln Val Val Thr Pro Pro Arg Glu Ser Ile  
 405 410 415  
 Gln Ala Ser Arg Gly Gln Thr Val Thr Phe Thr Cys Val Ala Ile Gly  
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Val Pro Ala Pro Phe Leu Ile Asn Trp Arg Leu Asn Trp Gly His Ile  
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 Pro Ser Gln Pro Arg Val Thr Val Thr Ser Glu Gly Gly Arg Gly Thr  
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 485 490 495  
 Leu Glu Leu Val Pro Gln Arg Ala Gly Pro Cys Pro Asp Gly His Phe  
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 Tyr Leu Glu His Ser Ala Ala Cys Leu Pro Cys Phe Cys Phe Gly Ile  
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 Arg Phe Asp Gln Pro Asp Asp Phe Lys Gly Val Asn Val Thr Met Pro  
 545 550 555 560  
 Ala Gln Pro Gly Thr Pro Pro Leu Ser Ser Thr Gln Leu Gln Ile Asp  
 565 570 575  
 Pro Ser Leu His Glu Phe Gln Leu Val Asp Leu Ser Arg Arg Phe Leu  
 580 585 590  
 Val His Asp Ser Phe Trp Ala Leu Pro Glu Gln Phe Leu Gly Asn Lys  
 595 600 605  
 Val Asp Ser Tyr Gly Gly Ser Leu Arg Tyr Asn Val Arg Tyr Glu Leu  
 610 615 620  
 Ala Arg Gly Met Leu Glu Pro Val Gln Arg Pro Asp Val Val Leu Val  
 625 630 635 640  
 Gly Ala Gly Tyr Arg Leu Leu Ser Arg Gly His Thr Pro Thr Gln Pro  
 645 650 655  
 Gly Ala Leu Asn Gln Arg Gln Val Gln Phe Ser Glu Glu His Trp Val  
 660 665 670  
 His Glu Ser Gly Arg Pro Val Gln Arg Ala Glu Leu Leu Gln Val Leu  
 675 680 685  
 Gln Ser Leu Glu Ala Val Leu Ile Gln Thr Val Tyr Asn Thr Lys Met  
 690 695 700  
 Ala Ser Val Gly Leu Ser Asp Ile Ala Met Asp Thr Thr Val Thr His  
 705 710 715 720  
 Ala Thr Ser His Gly Arg Ala His Ser Val Glu Glu Cys Arg Cys Pro  
 725 730 735  
 Ile Gly Tyr Ser Gly Leu Ser Cys Glu Ser Cys Asp Ala His Phe Thr  
 740 745 750  
 Arg Val Pro Gly Gly Pro Tyr Leu Gly Thr Cys Ser Gly Cys Ser Cys



755					760					765					
Asn	Gly	His	Ala	Ser	Ser	Cys	Asp	Pro	Val	Tyr	Gly	His	Cys	Leu	Asn
770						775					780				
Cys	Gln	His	Asn	Thr	Glu	Gly	Pro	Gln	Cys	Lys	Lys	Cys	Lys	Ala	Gly
785					790					795					800
Phe	Phe	Gly	Asp	Ala	Met	Lys	Ala	Thr	Ala	Thr	Ser	Cys	Arg	Pro	Cys
				805					810					815	
Pro	Cys	Pro	Tyr	Ile	Asp	Ala	Ser	Arg	Arg	Phe	Ser	Asp	Thr	Cys	Phe
			820					825					830		
Leu	Asp	Thr	Asp	Gly	Gln	Ala	Thr	Cys	Asp	Ala	Cys	Ala	Pro	Gly	Tyr
		835					840					845			
Thr	Gly	Arg	Arg	Cys	Glu	Ser	Cys	Ala	Pro	Gly	Tyr	Glu	Gly	Asn	Pro
	850					855					860				
Ile	Gln	Pro	Gly	Gly	Lys	Cys	Arg	Pro	Val	Asn	Gln	Glu	Ile	Val	Arg
865					870					875					880
Cys	Asp	Glu	Arg	Gly	Ser	Met	Gly	Thr	Ser	Gly	Glu	Ala	Cys	Arg	Cys
				885					890					895	
Lys	Asn	Asn	Val	Val	Gly	Arg	Leu	Cys	Asn	Glu	Cys	Ala	Asp	Arg	Ser
			900					905					910		
Phe	His	Leu	Ser	Thr	Arg	Asn	Pro	Asp	Gly	Cys	Leu	Lys	Cys	Phe	Cys
		915					920					925			
Met	Gly	Val	Ser	Arg	His	Cys	Thr	Ser	Ser	Ser	Trp	Ser	Arg	Ala	Gln
	930					935					940				
Leu	His	Gly	Ala	Ser	Glu	Glu	Pro	Gly	His	Phe	Ser	Leu	Thr	Asn	Ala
945					950					955					960
Ala	Ser	Thr	His	Thr	Thr	Asn	Glu	Gly	Ile	Phe	Ser	Pro	Thr	Pro	Gly
				965					970					975	
Glu	Leu	Gly	Phe	Ser	Ser	Phe	His	Arg	Leu	Leu	Ser	Gly	Pro	Tyr	Phe
			980					985					990		
Trp	Ser	Leu	Pro	Ser	Arg	Phe	Leu	Gly	Asp	Lys	Val	Thr	Ser	Tyr	Gly
		995					1000					1005			
Gly	Glu	Leu	Arg	Phe	Thr	Val	Thr	Gln	Arg	Ser	Gln	Pro	Gly	Ser	Thr
	1010					1015					1020				
Pro	Leu	His	Gly	Gln	Pro	Leu	Val	Val	Leu	Gln	Gly	Asn	Asn	Ile	Ile
	1025					1030					1035				1040
Leu	Glu	His	His	Val	Ala	Gln	Glu	Pro	Ser	Pro	Gly	Gln	Pro	Ser	Thr
			1045					1050					1055		
Phe	Ile	Val	Pro	Phe	Arg	Glu	Gln	Ala	Trp	Gln	Arg	Pro	Asp	Gly	Gln
			1060					1065					1070		
Pro	Ala	Thr	Arg	Glu	His	Leu	Leu	Met	Ala	Leu	Ala	Gly	Ile	Asp	Thr
		1075					1080					1085			

Leu	Leu	Ile	Arg	Ala	Ser	Tyr	Ala	Gln	Gln	Pro	Ala	Glu	Ser	Arg	Val	
1090				1095				1100								
Ser	Gly	Ile	Ser	Met	Asp	Val	Ala	Val	Pro	Glu	Glu	Thr	Gly	Gln	Asp	
1105				1110				1115				1120				
Pro	Ala	Leu	Glu	Val	Glu	Gln	Cys	Ser	Cys	Pro	Pro	Gly	Tyr	Arg	Gly	
				1125				1130				1135				
Pro	Ser	Cys	Gln	Asp	Cys	Asp	Thr	Gly	Tyr	Thr	Arg	Thr	Pro	Ser	Gly	
				1140				1145				1150				
Leu	Tyr	Leu	Gly	Thr	Cys	Glu	Arg	Cys	Ser	Cys	His	Gly	His	Ser	Glu	
1155				1160				1165								
Ala	Cys	Glu	Pro	Glu	Thr	Gly	Ala	Cys	Gln	Gly	Cys	Gln	His	His	Thr	
1170				1175				1180								
Glu	Gly	Pro	Arg	Cys	Glu	Gln	Cys	Gln	Pro	Gly	Tyr	Tyr	Gly	Asp	Ala	
1185				1190				1195				1200				
Gln	Arg	Gly	Thr	Pro	Gln	Asp	Cys	Gln	Leu	Cys	Pro	Cys	Tyr	Gly	Asp	
				1205				1210				1215				
Pro	Ala	Ala	Gly	Gln	Ala	Ala	His	Thr	Cys	Phe	Leu	Asp	Thr	Asp	Gly	
				1220				1225				1230				
His	Pro	Thr	Cys	Asp	Ala	Cys	Ser	Pro	Gly	His	Ser	Gly	Arg	His	Cys	
1235				1240				1245								
Glu	Arg	Cys	Ala	Pro	Gly	Tyr	Tyr	Gly	Asn	Pro	Ser	Gln	Gly	Gln	Pro	
1250				1255				1260								
Cys	Gln	Arg	Asp	Ser	Gln	Val	Pro	Gly	Pro	Ile	Gly	Cys	Asn	Cys	Asp	
1265				1270				1275				1280				
Pro	Gln	Gly	Ser	Val	Ser	Ser	Gln	Cys	Asp	Ala	Ala	Gly	Gln	Cys	Gln	
				1285				1290				1295				
Cys	Lys	Ala	Gln	Val	Glu	Gly	Leu	Thr	Cys	Ser	His	Cys	Arg	Pro	His	
1300				1305				1310								
His	Phe	His	Leu	Ser	Ala	Ser	Asn	Pro	Asp	Gly	Cys	Leu	Pro	Cys	Phe	
1315				1320				1325								
Cys	Met	Gly	Ile	Thr	Gln	Gln	Cys	Ala	Ser	Ser	Ala	Tyr	Thr	Arg	His	
1330				1335				1340								
Leu	Ile	Ser	Thr	His	Phe	Ala	Pro	Gly	Asp	Phe	Gln	Gly	Phe	Ala	Leu	
1345				1350				1355				1360				
Val	Asn	Pro	Gln	Arg	Asn	Ser	Arg	Leu	Thr	Gly	Glu	Phe	Thr	Val	Glu	
				1365				1370				1375				
Pro	Val	Pro	Glu	Gly	Ala	Gln	Leu	Ser	Phe	Gly	Asn	Phe	Ala	Gln	Leu	
1380				1385				1390								
Gly	His	Glu	Ser	Phe	Tyr	Trp	Gln	Leu	Pro	Glu	Thr	Tyr	Gln	Gly	Asp	
1395				1400				1405								

Lys Val Ala Ala Tyr Gly Gly Lys Leu Arg Tyr Thr Leu Ser Tyr Thr  
 1410 1415 1420  
 Ala Gly Pro Gln Gly Ser Pro Leu Ser Asp Pro Asp Val Gln Ile Thr  
 1425 1430 1435 1440  
 Gly Asn Asn Ile Met Leu Val Ala Ser Gln Pro Ala Leu Gln Gly Pro  
 1445 1450 1455  
 Glu Arg Arg Ser Tyr Glu Ile Met Phe Arg Glu Glu Phe Trp Arg Arg  
 1460 1465 1470  
 Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu Ala  
 1475 1480 1485  
 Asp Leu Asp Glu Leu Leu Ile Arg Ala Thr Phe Ser Ser Val Pro Leu  
 1490 1495 1500  
 Val Ala Ser Ile Ser Ala Val Ser Leu Glu Val Ala Gln Pro Gly Pro  
 1505 1510 1515 1520  
 Ser Asn Arg Pro Arg Ala Leu Glu Val Glu Glu Cys Arg Cys Pro Pro  
 1525 1530 1535  
 Gly Tyr Ile Gly Leu Ser Cys Gln Asp Cys Ala Pro Gly Tyr Thr Arg  
 1540 1545 1550  
 Thr Gly Ser Gly Leu Tyr Leu Gly His Cys Glu Leu Cys Glu Cys Asn  
 1555 1560 1565  
 Gly His Ser Asp Leu Cys His Pro Glu Thr Gly Ala Cys Ser Gln Cys  
 1570 1575 1580  
 Gln His Asn Ala Ala Gly Glu Phe Cys Glu Leu Cys Ala Pro Gly Tyr  
 1585 1590 1595 1600  
 Tyr Gly Asp Ala Thr Ala Gly Thr Pro Glu Asp Cys Gln Pro Cys Ala  
 1605 1610 1615  
 Cys Pro Leu Thr Asn Pro Glu Asn Met Phe Ser Arg Thr Cys Glu Ser  
 1620 1625 1630  
 Leu Gly Ala Gly Gly Tyr Arg Cys Thr Ala Cys Glu Pro Gly Tyr Thr  
 1635 1640 1645  
 Gly Gln Tyr Cys Glu Gln Cys Gly Pro Gly Tyr Val Gly Asn Pro Ser  
 1650 1655 1660  
 Val Gln Gly Gly Gln Cys Leu Pro Glu Thr Asn Gln Ala Pro Leu Val  
 1665 1670 1675 1680  
 Val Glu Val His Pro Ala Arg Ser Ile Val Pro Gln Gly Gly Ser His  
 1685 1690 1695  
 Ser Leu Arg Cys Gln Val Ser Gly Arg Gly Pro His Tyr Phe Tyr Trp  
 1700 1705 1710  
 Ser Arg Glu Asp Gly Arg Pro Val Pro Ser Gly Thr Gln Gln Arg His  
 1715 1720 1725  
 Gln Gly Ser Glu Leu His Phe Pro Ser Val Gln Pro Ser Asp Ala Gly

1730				1735				1740							
Val 1745	Tyr	Ile	Cys	Thr	Cys	Arg	Asn	Leu	His	Arg	Ser	Asn	Thr	Ser	Arg 1760
				1750				1755							
Ala	Glu	Leu	Leu	Val	Thr	Glu	Ala	Pro	Ser	Lys	Pro	Ile	Thr	Val	Thr 1775
				1765				1770							
Val	Glu	Glu	Gln	Arg	Ser	Gln	Ser	Val	Arg	Pro	Gly	Ala	Asp	Val	Thr 1790
				1780				1785							
Phe	Ile	Cys	Thr	Ala	Lys	Ser	Lys	Ser	Pro	Ala	Tyr	Thr	Leu	Val	Trp
				1795				1800				1805			
Thr	Arg	Leu	His	Asn	Gly	Lys	Leu	Pro	Thr	Arg	Ala	Met	Asp	Phe	Asn
				1810				1815				1820			
Gly	Ile	Leu	Thr	Ile	Arg	Asn	Val	Gln	Leu	Ser	Asp	Ala	Gly	Thr	Tyr 1840
				1830				1835							
Val	Cys	Thr	Gly	Ser	Asn	Met	Phe	Ala	Met	Asp	Gln	Gly	Thr	Ala	Thr
				1845				1850				1855			
Leu	His	Val	Gln	Ala	Ser	Gly	Thr	Leu	Ser	Ala	Pro	Val	Val	Ser	Ile
				1860				1865				1870			
His	Pro	Pro	Gln	Leu	Thr	Val	Gln	Pro	Gly	Gln	Leu	Ala	Glu	Phe	Arg
				1875				1880				1885			
Cys	Ser	Ala	Thr	Gly	Ser	Pro	Thr	Pro	Thr	Leu	Glu	Trp	Thr	Gly	Gly
				1890				1895				1900			
Pro	Gly	Gly	Gln	Leu	Pro	Ala	Lys	Ala	Gln	Ile	His	Gly	Gly	Ile	Leu 1920
				1910				1915							
Arg	Leu	Pro	Ala	Val	Glu	Pro	Thr	Asp	Gln	Ala	Gln	Tyr	Leu	Cys	Arg
				1925				1930				1935			
Ala	His	Ser	Ser	Ala	Gly	Gln	Gln	Val	Ala	Arg	Ala	Val	Leu	His	Val
				1940				1945				1950			
His	Gly	Gly	Gly	Gly	Pro	Arg	Val	Gln	Val	Ser	Pro	Glu	Arg	Thr	Gln
				1955				1960				1965			
Val	His	Ala	Gly	Arg	Thr	Val	Arg	Leu	Tyr	Cys	Arg	Ala	Ala	Gly	Val
				1970				1975				1980			
Pro	Ser	Ala	Thr	Ile	Thr	Trp	Arg	Lys	Glu	Gly	Gly	Ser	Leu	Pro	Pro 2000
				1990				1995							
Gln	Ala	Arg	Ser	Glu	Arg	Thr	Asp	Ile	Ala	Thr	Leu	Leu	Ile	Pro	Ala
				2005				2010				2015			
Ile	Thr	Thr	Ala	Asp	Ala	Gly	Phe	Tyr	Leu	Cys	Val	Ala	Thr	Ser	Pro
				2020				2025				2030.			
Ala	Gly	Thr	Ala	Gln	Ala	Arg	Ile	Gln	Val	Val	Val	Leu	Ser	Ala	Ser
				2035				2040				2045			
Asp	Ala	Ser	Gln	Pro	Pro	Val	Lys	Ile	Glu	Ser	Ser	Ser	Pro	Ser	Val
				2050				2055				2060			

Thr	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Val	Val	Ala	Gly	Ser	Ala	
2065							2070				2075					2080
His	Ala	Gln	Val	Thr	Trp	Tyr	Arg	Arg	Gly	Gly	Ser	Leu	Pro	His	His	
				2085					2090					2095		
Thr	Gln	Val	His	Gly	Ser	Arg	Leu	Arg	Leu	Pro	Gln	Val	Ser	Pro	Ala	
			2100					2105					2110			
Asp	Ser	Gly	Glu	Tyr	Val	Cys	Arg	Val	Glu	Asn	Gly	Ser	Gly	Pro	Lys	
		2115					2120					2125				
Glu	Ala	Ser	Ile	Thr	Val	Ser	Val	Leu	His	Gly	Thr	His	Ser	Gly	Pro	
	2130					2135					2140					
Ser	Tyr	Thr	Pro	Val	Pro	Gly	Ser	Thr	Arg	Pro	Ile	Arg	Ile	Glu	Pro	
2145					2150					2155					2160	
Ser	Ser	Ser	His	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Val	
			2165					2170					2175			
Val	Pro	Gly	Gln	Ala	His	Ala	Gln	Val	Thr	Trp	His	Lys	Arg	Gly	Gly	
			2180					2185					2190			
Ser	Leu	Pro	Ala	Arg	His	Gln	Thr	His	Gly	Ser	Leu	Leu	Arg	Leu	His	
	2195						2200					2205				
Gln	Val	Thr	Pro	Ala	Asp	Ser	Gly	Glu	Tyr	Val	Cys	His	Val	Val	Gly	
	2210					2215					2220					
Thr	Ser	Gly	Pro	Leu	Glu	Ala	Ser	Val	Leu	Val	Thr	Ile	Glu	Ala	Ser	
2225					2230					2235					2240	
Val	Ile	Pro	Gly	Pro	Ile	Pro	Pro	Val	Arg	Ile	Glu	Ser	Ser	Ser	Ser	
				2245					2250					2255		
Thr	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Ser	Cys	Val	Val	Ala	Gly	
		2260					2265						2270			
Gln	Ala	His	Ala	Gln	Val	Thr	Trp	Tyr	Lys	Arg	Gly	Gly	Ser	Leu	Pro	
		2275					2280					2285				
Ala	Arg	His	Gln	Val	Arg	Gly	Ser	Arg	Leu	Tyr	Ile	Phe	Gln	Ala	Ser	
	2290					2295					2300					
Pro	Ala	Asp	Ala	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Ser	Asn	Gly	Met	Glu	
2305					2310					2315					2320	
Ala	Ser	Ile	Thr	Val	Thr	Val	Thr	Gly	Thr	Gln	Gly	Ala	Asn	Leu	Ala	
				2325					2330					2335		
Tyr	Pro	Ala	Gly	Ser	Thr	Gln	Pro	Ile	Arg	Ile	Glu	Pro	Ser	Ser	Ser	
		2340						2345					2350			
Gln	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Val	Val	Pro	Gly	
		2355					2360					2365				
Gln	Ser	His	Ala	Gln	Val	Thr	Trp	His	Lys	Arg	Gly	Gly	Ser	Leu	Pro	
	2370					2375					2380					

Val	Arg	His	Gln	Thr	His	Gly	Ser	Leu	Arg	Leu	Tyr	Gln	Ala	Ser	
2385					2390					2395				2400	
Pro	Ala	Asp	Ser	Gly	Glu	Tyr	Val	Cys	Arg	Val	Leu	Gly	Ser	Ser	Val
				2405					2410					2415	
Pro	Leu	Glu	Ala	Ser	Val	Leu	Val	Thr	Ile	Glu	Pro	Ala	Gly	Ser	Val
			2420					2425					2430		
Pro	Ala	Leu	Gly	Val	Thr	Pro	Thr	Val	Arg	Ile	Glu	Ser	Ser	Ser	Ser
		2435					2440					2445			
Gln	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Leu	Val	Ala	Gly
	2450					2455					2460				
Gln	Ala	His	Ala	Gln	Val	Thr	Trp	His	Lys	Arg	Gly	Gly	Ser	Leu	Pro
2465					2470					2475					2480
Ala	Arg	His	Gln	Val	His	Gly	Ser	Arg	Leu	Arg	Leu	Leu	Gln	Val	Thr
			2485						2490					2495	
Pro	Ala	Asp	Ser	Gly	Glu	Tyr	Val	Cys	Arg	Val	Val	Gly	Ser	Ser	Gly
			2500					2505					2510		
Thr	Gln	Glu	Ala	Ser	Val	Leu	Val	Thr	Ile	Gln	Gln	Arg	Leu	Ser	Gly
	2515						2520					2525			
Ser	His	Ser	Gln	Gly	Val	Ala	Tyr	Pro	Val	Arg	Ile	Glu	Ser	Ser	Ser
	2530					2535					2540				
Ala	Ser	Leu	Ala	Asn	Gly	His	Thr	Leu	Asp	Leu	Asn	Cys	Leu	Val	Ala
2545					2550					2555					2560
Ser	Gln	Ala	Pro	His	Thr	Ile	Thr	Trp	Tyr	Lys	Arg	Gly	Gly	Ser	Leu
			2565						2570					2575	
Pro	Ser	Arg	His	Gln	Ile	Val	Gly	Ser	Arg	Leu	Arg	Ile	Pro	Gln	Val
			2580					2585					2590		
Thr	Pro	Ala	Asp	Ser	Gly	Glu	Tyr	Val	Cys	His	Val	Ser	Asn	Gly	Ala
	2595						2600					2605			
Gly	Ser	Arg	Glu	Thr	Ser	Leu	Ile	Val	Thr	Ile	Gln	Gly	Ser	Gly	Ser
	2610					2615					2620				
Ser	His	Val	Pro	Arg	Val	Ser	Pro	Pro	Ile	Arg	Ile	Glu	Ser	Ser	Ser
2625					2630					2635					2640
Pro	Thr	Val	Val	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Val	Val	Ala
			2645						2650					2655	
Arg	Gln	Pro	Gln	Ala	Ile	Ile	Thr	Trp	Tyr	Lys	Arg	Gly	Gly	Ser	Leu
		2660						2665					2670		
Pro	Ser	Arg	His	Gln	Thr	His	Gly	Ser	His	Leu	Arg	Leu	His	Gln	Met
		2675					2680					2685			
Ser	Val	Ala	Asp	Ser	Gly	Glu	Tyr	Val	Cys	Arg	Ala	Asn	Asn	Asn	Ile
	2690					2695					2700				
Asp	Ala	Leu	Glu	Ala	Ser	Ile	Val	Ile	Ser	Val	Ser	Pro	Ser	Ala	Glu

2705                      2710                      2715                      2720

Ser Pro Ser Ala Pro Gly Ser Ser Met Pro Ile Arg Ile Glu Ser Ser  
                                 2725                      2730                      2735

Ser Ser His Val Ala Glu Gly Glu Thr Leu Asp Leu Asn Cys Val Val  
                                 2740                      2745                      2750

Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser  
                                 2755                      2760                      2765

Leu Pro Ser Tyr His Gln Thr Arg Gly Ser Arg Leu Arg Leu His His  
                                 2770                      2775                      2780

Val Ser Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Met Gly Ser  
2785                      2790                      2795                      2800

Ser Gly Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Ala Ser Gly  
                                 2805                      2810                      2815

Ser Ser Ala Val His Val Pro Ala Pro Gly Gly Ala Pro Pro Ile Arg  
                                 2820                      2825                      2830

Ile Glu Pro Ser Ser Ser Arg Val Ala Glu Gly Gln Thr Leu Asp Leu  
                                 2835                      2840                      2845

Lys Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys  
                                 2850                      2855                      2860

Arg Gly Gly Asn Leu Pro Ala Arg His Gln Val His Gly Pro Leu Leu  
2865                      2870                      2875                      2880

Arg Leu Asn Gln Val Ser Pro Ala Asp Ser Gly Glu Tyr Ser Cys Gln  
                                 2885                      2890                      2895

Val Thr Gly Ser Ser Gly Thr Leu Glu Ala Ser Val Leu Val Thr Ile  
                                 2900                      2905                      2910

Glu Pro Ser Ser Pro Gly Pro Ile Pro Ala Pro Gly Leu Ala Gln Pro  
                                 2915                      2920                      2925

Ile Tyr Ile Glu Ala Ser Ser Ser His Val Thr Glu Gly Gln Thr Leu  
2930                      2935                      2940

Asp Leu Asn Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp  
2945                      2950                      2955                      2960

Tyr Lys Arg Gly Gly Ser Leu Pro Ala Arg His Gln Thr His Gly Ser  
                                 2965                      2970                      2975

Gln Leu Arg Leu His His Val Ser Pro Ala Asp Ser Gly Glu Tyr Val  
                                 2980                      2985                      2990

Cys Arg Ala Ala Gly Gly Pro Gly Pro Glu Gln Glu Ala Ser Phe Thr  
                                 2995                      3000                      3005

Val Thr Val Pro Pro Ser Glu Gly Ser Ser Tyr Arg Leu Arg Ser Pro  
3010                      3015                      3020

Val Ile Ser Ile Asp Pro Pro Ser Ser Thr Val Gln Gln Gly Gln Asp  
3025                      3030                      3035                      3040

Ala Ser Phe Lys Cys Leu Ile His Asp Gly Ala Ala Pro Ile Ser Leu  
3045 3050 3055

Glu Trp Lys Thr Arg Asn Gln Glu Leu Glu Asp Asn Val His Ile Ser  
3060 3065 3070

Pro Asn Gly Ser Ile Ile Thr Ile Val Gly Thr Arg Pro Ser Asn His  
3075 3080 3085

Gly Thr Tyr Arg Cys Val Ala Ser Asn Ala Tyr Gly Val Ala Gln Ser  
3090 3095 3100

Val Val Asn Leu Ser Val His Gly Pro Pro Thr Val Ser Val Leu Pro  
3105 3110 3115 3120

Glu Gly Pro Val Trp Val Lys Val Gly Lys Ala Val Thr Leu Glu Cys  
3125 3130 3135

Val Ser Ala Gly Glu Pro Arg Ser Ser Ala Arg Trp Thr Arg Ile Ser  
3140 3145 3150

Ser Thr Pro Ala Lys Leu Glu Gln Arg Thr Tyr Gly Leu Met Asp Ser  
3155 3160 3165

His Thr Val Leu Gln Ile Ser Ser Ala Lys Pro Ser Asp Ala Gly Thr  
3170 3175 3180

Tyr Val Cys Leu Ala Gln Asn Ala Leu Gly Thr Ala Gln Lys Gln Val  
3185 3190 3195 3200

Glu Val Ile Val Asp Thr Gly Ala Met Ala Pro Gly Ala Pro Gln Val  
3205 3210 3215

Gln Ala Glu Glu Ala Glu Leu Thr Val Glu Ala Gly His Thr Ala Thr  
3220 3225 3230

Leu Arg Cys Ser Ala Thr Gly Ser Pro Ala Arg Thr Ile His Trp Ser  
3235 3240 3245

Lys Leu Arg Ser Pro Leu Pro Trp Gln His Arg Leu Glu Gly Asp Thr  
3250 3255 3260

Leu Ile Ile Pro Arg Val Ala Gln Gln Asp Ser Gly Gln Tyr Ile Cys  
3265 3270 3275 3280

Asn Ala Thr Ser Pro Ala Gly His Ala Glu Ala Thr Ile Ile Leu His  
3285 3290 3295

Val Glu Ser Pro Pro Tyr Ala Thr Thr Val Pro Glu His Ala Ser Val  
3300 3305 3310

Gln Ala Gly Glu Thr Val Gln Leu Gln Cys Leu Ala His Gly Thr Pro  
3315 3320 3325

Pro Leu Thr Phe Gln Trp Ser Arg Val Gly Ser Ser Leu Pro Gly Arg  
3330 3335 3340

Ala Thr Ala Arg Asn Glu Leu Leu His Phe Glu Arg Ala Ala Pro Glu  
3345 3350 3355 3360



Asp Ser Gly Arg Tyr Arg Cys Arg Val Thr Asn Lys Val Gly Ser Ala  
3365 3370 3375

Glu Ala Phe Ala Gln Leu Leu Val Gln Gly Pro Pro Gly Ser Leu Pro  
3380 3385 3390

Ala Thr Ser Ile Pro Ala Gly Ser Thr Pro Thr Val Gln Val Thr Pro  
3395 3400 3405

Gln Leu Glu Thr Lys Ser Ile Gly Ala Ser Val Glu Phe His Cys Ala  
3410 3415 3420

Val Pro Ser Asp Arg Gly Thr Gln Leu Arg Trp Phe Lys Glu Gly Gly  
3425 3430 3435 3440

Gln Leu Pro Pro Gly His Ser Val Gln Asp Gly Val Leu Arg Ile Gln  
3445 3450 3455

Asn Leu Asp Gln Ser Cys Gln Gly Thr Tyr Ile Cys Gln Ala His Gly  
3460 3465 3470

Pro Trp Gly Lys Ala Gln Ala Ser Ala Gln Leu Val Ile Gln Ala Leu  
3475 3480 3485

Pro Ser Val Leu Ile Asn Ile Arg Thr Ser Val Gln Thr Val Val Val  
3490 3495 3500

Gly His Ala Val Glu Phe Glu Cys Leu Ala Leu Gly Asp Pro Lys Pro  
3505 3510 3515 3520

Gln Val Thr Trp Ser Lys Val Gly Gly His Leu Arg Pro Gly Ile Val  
3525 3530 3535

Gln Ser Gly Gly Val Val Arg Ile Ala His Val Glu Leu Ala Asp Ala  
3540 3545 3550

Gly Gln Tyr Arg Cys Thr Ala Thr Asn Ala Ala Gly Thr Thr Gln Ser  
3555 3560 3565

His Val Leu Leu Leu Val Gln Ala Leu Pro Gln Ile Ser Met Pro Gln  
3570 3575 3580

Glu Val Arg Val Pro Ala Gly Ser Ala Ala Val Phe Pro Cys Ile Ala  
3585 3590 3595 3600

Ser Gly Tyr Pro Thr Pro Asp Ile Ser Trp Ser Lys Leu Asp Gly Ser  
3605 3610 3615

Leu Pro Pro Asp Ser Arg Leu Glu Asn Asn Met Leu Met Leu Pro Ser  
3620 3625 3630

Val Gln Pro Gln Asp Ala Gly Thr Tyr Val Cys Thr Ala Thr Asn Arg  
3635 3640 3645

Gln Gly Lys Val Lys Ala Phe Ala His Leu Gln Val Pro Glu Arg Val  
3650 3655 3660

Val Pro Tyr Phe Thr Gln Thr Pro Tyr Ser Phe Leu Pro Leu Pro Thr  
3665 3670 3675 3680

Ile Lys Asp Ala Tyr Arg Lys Phe Glu Ile Lys Ile Thr Phe Arg Pro

3685										3690					3695				
Asp	Ser	Ala	Asp	Gly	Met	Leu	Leu	Tyr	Asn	Gly	Gln	Lys	Arg	Val	Pro				
3700				3705						3710									
Gly	Ser	Pro	Thr	Asn	Leu	Ala	Asn	Arg	Gln	Pro	Asp	Phe	Ile	Ser	Phe				
3715				3720						3725									
Gly	Leu	Val	Gly	Gly	Arg	Pro	Glu	Phe	Arg	Phe	Asp	Ala	Gly	Ser	Gly				
3730				3735						3740									
Met	Ala	Thr	Ile	Arg	His	Pro	Thr	Pro	Leu	Ala	Leu	Gly	His	Phe	His				
3745				3750						3755						3760			
Thr	Val	Thr	Leu	Leu	Arg	Ser	Leu	Thr	Gln	Gly	Ser	Leu	Ile	Val	Gly				
3765				3770						3775									
Asp	Leu	Ala	Pro	Val	Asn	Gly	Thr	Ser	Gln	Gly	Lys	Phe	Gln	Gly	Leu				
3780				3785						3790									
Asp	Leu	Asn	Glu	Glu	Leu	Tyr	Leu	Gly	Gly	Tyr	Pro	Asp	Tyr	Gly	Ala				
3795				3800						3805									
Ile	Pro	Lys	Ala	Gly	Leu	Ser	Ser	Gly	Phe	Ile	Gly	Cys	Val	Arg	Glu				
3810				3815						3820									
Leu	Arg	Ile	Gln	Gly	Glu	Glu	Ile	Val	Phe	His	Asp	Leu	Asn	Leu	Thr				
3825				3830						3835						3840			
Ala	His	Gly	Ile	Ser	His	Cys	Pro	Thr	Cys	Arg	Asp	Arg	Pro	Cys	Gln				
3845				3850						3855									
Asn	Gly	Gly	Gln	Cys	His	Asp	Ser	Glu	Ser	Ser	Ser	Tyr	Val	Cys	Val				
3860				3865						3870									
Cys	Pro	Ala	Gly	Phe	Thr	Gly	Ser	Arg	Cys	Glu	His	Ser	Gln	Ala	Leu				
3875				3880						3885									
His	Cys	His	Pro	Glu	Ala	Cys	Gly	Pro	Asp	Ala	Thr	Cys	Val	Asn	Arg				
3890				3895						3900									
Pro	Asp	Gly	Arg	Gly	Tyr	Thr	Cys	Arg	Cys	His	Leu	Gly	Arg	Ser	Gly				
3905				3910						3915						3920			
Leu	Arg	Cys	Glu	Glu	Gly	Val	Thr	Val	Thr	Thr	Pro	Ser	Leu	Ser	Gly				
3925				3930						3935									
Ala	Gly	Ser	Tyr	Leu	Ala	Leu	Pro	Ala	Leu	Thr	Asn	Thr	His	His	Glu				
3940				3945						3950									
Leu	Arg	Leu	Asp	Val	Glu	Phe	Lys	Pro	Leu	Ala	Pro	Asp	Gly	Val	Leu				
3955				3960						3965									
Leu	Phe	Ser	Gly	Gly	Lys	Ser	Gly	Pro	Val	Glu	Asp	Phe	Val	Ser	Leu				
3970				3975						3980									
Ala	Met	Val	Gly	Gly	His	Leu	Glu	Phe	Arg	Tyr	Glu	Leu	Gly	Ser	Gly				
3985				3990						3995						4000			
Leu	Ala	Val	Leu	Arg	Thr	Ala	Glu	Pro	Leu	Ala	Leu	Gly	Arg	Trp	His				
4005				4010						4015									

Arg Val Ser Ala Glu Arg Leu Asn Lys Asp Gly Ser Leu Arg Val Asn  
 4020 4025 4030  
 Gly Gly Arg Pro Val Leu Arg Ser Ser Pro Gly Lys Ser Gln Gly Leu  
 4035 4040 4045  
 Asn Leu His Thr Leu Leu Tyr Leu Gly Gly Val Glu Pro Ser Val Pro  
 4050 4055 4060  
 Leu Ser Pro Ala Thr Asn Met Ser Ala His Phe Arg Gly Cys Val Gly  
 4065 4070 4075 4080  
 Glu Val Ser Val Asn Gly Lys Arg Leu Asp Leu Thr Tyr Ser Phe Leu  
 4085 4090 4095  
 Gly Ser Gln Gly Ile Gly Gln Cys Tyr Asp Ser Ser Pro Cys Glu Arg  
 4100 4105 4110  
 Gln Pro Cys Gln His Gly Ala Thr Cys Met Pro Ala Gly Glu Tyr Glu  
 4115 4120 4125  
 Phe Gln Cys Leu Cys Arg Asp Gly Ile Lys Gly Asp Leu Cys Glu His  
 4130 4135 4140  
 Glu Glu Asn Pro Cys Gln Leu Arg Glu Pro Cys Leu His Gly Gly Thr  
 4145 4150 4155 4160  
 Cys Gln Gly Thr Arg Cys Leu Cys Leu Pro Gly Phe Ser Gly Pro Arg  
 4165 4170 4175  
 Cys Gln Gln Gly Ser Gly His Gly Ile Ala Glu Ser Asp Trp His Leu  
 4180 4185 4190  
 Glu Gly Ser Gly Gly Asn Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe  
 4195 4200 4205  
 His Asp Asp Gly Phe Leu Ala Phe Pro Gly His Val Phe Ser Arg Ser  
 4210 4215 4220  
 Leu Pro Glu Val Pro Glu Thr Ile Glu Leu Glu Val Arg Thr Ser Thr  
 4225 4230 4235 4240  
 Ala Ser Gly Leu Leu Leu Trp Gln Gly Val Glu Val Gly Glu Ala Gly  
 4245 4250 4255  
 Gln Gly Lys Asp Phe Ile Ser Leu Gly Leu Gln Asp Gly His Leu Val  
 4260 4265 4270  
 Phe Arg Tyr Gln Leu Gly Ser Gly Glu Ala Arg Leu Val Ser Glu Asp  
 4275 4280 4285  
 Pro Ile Asn Asp Gly Glu Trp His Arg Val Thr Ala Leu Arg Glu Gly  
 4290 4295 4300  
 Arg Arg Gly Ser Ile Gln Val Asp Gly Glu Glu Leu Val Ser Gly Arg  
 4305 4310 4315 4320  
 Ser Pro Gly Pro Asn Val Ala Val Asn Ala Lys Gly Ser Ile Tyr Ile  
 4325 4330 4335

<210> 3  
<211> 508

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

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Arg Thr Cys Arg Cys Lys Asn Asn Val Val Gly Arg Leu Cys Asn Glu
 1          5          10          15

Cys Ala Asp Arg Ser Phe His Leu Ser Thr Arg Asn Pro Asp Gly Cys
      20          25          30

Leu Lys Cys Phe Cys Met Gly Val Ser Arg His Cys Thr Ser Ser Ser
      35          40          45

Trp Ser Arg Ala Gln Leu His Gly Ala Ser Glu Glu Pro Gly His Phe
 50          55          60

Ser Leu Thr Asn Ala Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe
 65          70          75          80

Ser Pro Thr Pro Gly Glu Leu Gly Phe Ser Ser Phe His Arg Leu Leu
      85          90          95

Ser Gly Pro Tyr Phe Trp Ser Leu Pro Ser Arg Phe Leu Gly Asp Lys
      100          105          110

Val Thr Ser Tyr Gly Gly Glu Leu Arg Phe Thr Val Thr Gln Arg Ser
      115          120          125

Gln Pro Gly Ser Thr Pro Leu His Gly Gln Pro Leu Val Val Leu Gln
      130          135          140

Gly Asn Asn Ile Ile Leu Glu His His Val Ala Gln Glu Pro Ser Pro
      145          150          155          160

Gly Gln Pro Ser Thr Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln
      165          170          175

Arg Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu
      180          185          190

Ala Gly Ile Asp Thr Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro
      195          200          205

Ala Glu Ser Arg Leu Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu
      210          215          220

Glu Thr Gly Gln Asp Pro Ala Leu Glu Val Glu Gln Cys Ser Cys Pro
      225          230          235          240

Pro Gly Tyr Leu Gly Pro Ser Cys Gln Asp Cys Asp Thr Gly Tyr Thr
      245          250          255

Arg Thr Pro Ser Gly Leu Tyr Leu Gly Thr Cys Glu Arg Cys Ser Cys
      260          265          270

His Gly His Ser Glu Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly
      275          280          285

Cys Gln His His Thr Glu Gly Pro Arg Cys Glu Gln Cys Gln Pro Gly
      290          295          300

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Tyr Tyr Gly Asp Ala Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys  
 305 310 315 320  
 Pro Cys Tyr Gly Asp Pro Ala Ala Gly Gln Ala Ala Leu Thr Cys Phe  
 325 330 335  
 Leu Asp Thr Asp Gly His Pro Thr Cys Asp Ala Cys Ser Pro Gly His  
 340 345 350  
 Ser Gly Arg His Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn Pro  
 355 360 365  
 Ser Gln Gly Gln Pro Cys Gln Arg Asp Ser Gln Val Pro Gly Pro Ile  
 370 375 380  
 Gly Cys Asn Cys Asp Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala  
 385 390 395 400  
 Ala Gly Gln Cys Gln Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser  
 405 410 415  
 His Cys Arg Pro His His Phe His Leu Ser Ala Ser Asn Pro Asp Gly  
 420 425 430  
 Cys Leu Pro Cys Phe Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser  
 435 440 445  
 Ala Tyr Thr Arg His Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe  
 450 455 460  
 Gln Gly Phe Ala Leu Val Asn Pro Gln Arg Asn Ser Arg Leu Thr Gly  
 465 470 475 480  
 Glu Phe Thr Val Glu Pro Val Pro Glu Gly Ala Gln Leu Ser Phe Gly  
 485 490 495  
 Asn Phe Ala Gln Leu Gly His Glu Ser Phe Tyr Trp  
 500 505

<210> 4  
 <211> 199  
 <212> PRT  
 <213> Homo sapiens

<400> 4  
 Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala  
 1 5 10 15  
 Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp  
 20 25 30  
 Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
 35 40 45  
 Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
 50 55 60  
 Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
 65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr  
                     85                    90                    95  
 Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe  
                     100                    105                    110  
 Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp  
                     115                    120                    125  
 Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr  
                     130                    135                    140  
 Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
                     145                    150                    155                    160  
 Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys  
                     165                    170                    175  
 Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
                     180                    185                    190  
 Arg Ser Glu Arg Asn Leu Leu  
                     195

<210> 5  
 <211> 199  
 <212> PRT  
 <213> Homo sapiens

<400> 5  
 Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala  
     1                    5                    10                    15  
 Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp  
                     20                    25                    30  
 Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
                     35                    40                    45  
 Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
                     50                    55                    60  
 Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
                     65                    70                    75                    80  
 Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr  
                     85                    90                    95  
 Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe  
                     100                    105                    110  
 Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp  
                     115                    120                    125  
 Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr  
                     130                    135                    140  
 Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
                     145                    150                    155                    160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys  
                           165                          170                          175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
                           180                          185                          190

Arg Ser Glu Arg Asn Leu Leu  
                           195

<210> 6  
 <211> 199  
 <212> PRT  
 <213> Homo sapiens

<400> 6  
 Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala  
   1                          5                          10                          15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp  
                           20                          25                          30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
                           35                          40                          45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
                           50                          55                          60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
   65                          70                          75                          80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr  
                           85                          90                          95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe  
                           100                          105                          110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp  
                           115                          120                          125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr  
                           130                          135                          140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
   145                          150                          155                          160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys  
                           165                          170                          175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
                           180                          185                          190

Arg Ser Glu Arg Asn Leu Leu  
                           195

<210> 7  
 <211> 182  
 <212> PRT  
 <213> Homo sapiens



Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp  
1 5 10 15

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
20 25 30

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
35 40 45

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
50 55 60

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr  
65 70 75 80

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe  
85 90 95

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp  
100 105 110

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr  
115 120 125

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
130 135 140

Pro	Pro	Glu	Ala	Gln	Lys	Ile	Val	Arg	Gln	Arg	Gln	Glu	Glu	Leu	Cys
145					150					155					160

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
165 170 175

Arg Ser Glu Arg Asn Leu  
180

<213> Homo sapiens

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys  
100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
180 185 190

Ile

<210> 9

<211> 193

<212> PRT

<213> Homo sapiens

<400> 9

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
20 25 30

Ser Phe Ser Trp Asp Asn Cys Phe Glu Gly Lys Asp Pro Ala Val Ile  
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys  
100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro  
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190

Ile

<210> 10  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens

<400> 10  
 Leu Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu  
 1 5 10 15  
 Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val  
 20 25 30  
 Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn  
 35 40 45  
 Val Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro  
 50 55 60  
 Leu Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile  
 65 70 75 80  
 Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe  
 85 90 95  
 Cys Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu  
 100 105 110  
 Pro Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly  
 115 120 125  
 Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu  
 130 135 140  
 Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser  
 145 150 155 160  
 Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys  
 165 170 175

Gly Ile

<210> 11  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens

<400> 11  
 Arg Ala Gly Pro Pro Phe Pro Met Gln Ser Leu Met Gln Ala Pro Leu  
 1 5 10 15  
 Leu Ile Ala Leu Gly Leu Leu Leu Ala Ala Pro Ala Gln Ala His Leu

20 25 30

Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu  
35 40 45

Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro  
50 55 60

Ile Ile Val Pro Gly Asn Val Thr Leu Ser Val Met Gly Ser Thr Ser  
65 70 75 80

Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu Val Leu Glu Lys Glu  
85 90 95

Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser  
100 105 110

Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp Met Leu Ile Pro Thr  
115 120 125

Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr Gly Leu Pro Cys His  
130 135 140

Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Lys Ser Glu Phe Val  
145 150 155 160

Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg  
165 170 175

Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys  
180 185 190

Ile Ala Ala Ser Leu Lys Gly Ile  
195 200

<210> 12  
<211> 189  
<212> PRT  
<213> Homo sapiens

<400> 12  
Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu Leu Ala Thr Pro  
1 5 10 15

Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp  
20 25 30

Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr  
35 40 45

Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val Thr Leu Ser Val  
50 55 60

Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu  
65 70 75 80

Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr  
85 90 95

Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp

	100		105		110										
Met	Leu	Ile	Pro	Thr	Gly	Glu	Pro	Cys	Pro	Glu	Pro	Leu	Arg	Thr	Tyr
	115						120					125			
Gly	Leu	Pro	Cys	His	Cys	Pro	Phe	Lys	Glu	Gly	Thr	Tyr	Ser	Leu	Pro
	130					135					140				
Lys	Ser	Glu	Phe	Val	Val	Pro	Asp	Leu	Glu	Leu	Pro	Ser	Trp	Leu	Thr
145					150					155					160
Thr	Gly	Asn	Tyr	Arg	Ile	Glu	Ser	Val	Leu	Ser	Ser	Ser	Gly	Lys	Arg
				165					170					175	
Leu	Gly	Cys	Ile	Lys	Ile	Ala	Ala	Ser	Leu	Lys	Gly	Ile			
			180					185							

<210> 13  
 <211> 193  
 <212> PRT  
 <213> Homo sapiens

<400> 13  
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
 1 5 10 15  
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
 20 25 30  
 Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
 35 40 45  
 Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
 50 55 60  
 Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
 65 70 75 80  
 Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
 85 90 95  
 Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys  
 100 105 110  
 Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
 115 120 125  
 Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
 130 135 140  
 Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
 145 150 155 160  
 Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
 165 170 175  
 Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190  
 Ile

<210> 14  
 <211> 193  
 <212> PRT  
 <213> Homo sapiens

<400> 14  
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
   1                  5                  10                  15  
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
                   20                  25                  30  
 Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
                   35                  40                  45  
 Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
                   50                  55                  60  
 Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
   65                  70                  75                  80  
 Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
                   85                  90                  95  
 Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys  
                   100                  105                  110  
 Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
                   115                  120                  125  
 Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
                   130                  135                  140  
 Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
   145                  150                  155                  160  
 Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
                   165                  170                  175  
 Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
                   180                  185                  190  
 Ile

<210> 15  
 <211> 193  
 <212> PRT  
 <213> Homo sapiens

<400> 15  
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
   1                  5                  10                  15  
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
                   20                  25                  30



Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
 115 120 125  
 Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
 130 135 140  
 Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
 145 150 155 160  
 Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
 165 170 175  
 Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190  
 Ile

<210> 17  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 17  
 Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile  
 1 5 10 15  
 Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu  
 20 25 30  
 Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe  
 35 40 45  
 Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu  
 50 55 60  
 Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe Ile  
 65 70 75 80  
 Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His Glu  
 85 90 95  
 Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu Gly  
 100 105 110  
 Thr Pro

<210> 18  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<400> 18  
 Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr  
 1 5 10 15  
 His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp  
 20 25 30



Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys  
                   35                  40                  45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly  
           50                  55                  60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val  
   65                  70                  75                  80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu  
                   85                  90

<210> 19  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<400> 19  
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His  
   1                  5                  10                  15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu  
           20                  25                  30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile  
           35                  40                  45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn  
   50                  55                  60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile  
   65                  70                  75                  80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu  
                   85                  90

<210> 20  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<400> 20  
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His  
   1                  5                  10                  15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu  
           20                  25                  30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile  
           35                  40                  45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn  
   50                  55                  60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile  
   65                  70                  75                  80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85

90

<210> 21  
 <211> 91  
 <212> PRT  
 <213> Homo sapiens

<400> 21  
 Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His Gln  
     1                    5                    10                    15  
 Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu Leu  
                     20                    25                    30  
 Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile Lys  
                     35                    40                    45  
 Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn Gln  
                     50                    55                    60  
 Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile Ala  
                     65                    70                    75                    80  
 Leu Lys Ala Ala His Tyr His Thr His Lys Glu  
                     85                    90

<210> 22  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<400> 22  
 Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr  
     1                    5                    10                    15  
 His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp  
                     20                    25                    30  
 Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys  
                     35                    40                    45  
 Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly  
                     50                    55                    60  
 Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val  
                     65                    70                    75                    80  
 Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu  
                     85                    90

<210> 23  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<400> 23  
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His  
     1                    5                    10                    15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu  
                     20                    25                    30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile  
                     35                    40                    45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn  
                     50                    55                    60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile  
                     65                    70                    75                    80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu  
                     85                    90

<210> 24  
 <211> 85  
 <212> PRT  
 <213> Homo sapiens

<400> 24  
 Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile  
   1                    5                    10                    15

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu  
                     20                    25                    30

His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile  
                     35                    40                    45

Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met  
                     50                    55                    60

Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly  
                     65                    70                    75                    80

Phe Cys Asp Glu Val  
                     85

<210> 25  
 <211> 381  
 <212> PRT  
 <213> Homo sapiens

<400> 25  
 Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Pro Thr  
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Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys  
                     20                    25                    30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln  
                     35                    40                    45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly  
                     50                    55                    60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn

65						70						75						80
Lys	Met	Ala	Lys	Glu	Ala	Ile	Phe	Gln	Asp	Thr	Met	Arg	Lys	Phe	Leu			
				85					90					95				
Glu	Gln	Glu	Cys	Asn	Val	Leu	Pro	Leu	Lys	Leu	Leu	Met	Pro	Gln	Cys			
				100					105					110				
Asn	Gln	Val	Leu	Asp	Asp	Tyr	Phe	Pro	Leu	Val	Ile	Asp	Tyr	Phe	Gln			
				115					120					125				
Asn	Gln	Ile	Asp	Ser	Asn	Gly	Ile	Cys	Met	His	Leu	Gly	Leu	Cys	Lys			
				130					135					140				
Ser	Arg	Gln	Pro	Glu	Pro	Glu	Gln	Glu	Pro	Gly	Met	Ser	Asp	Pro	Leu			
145					150					155					160			
Pro	Lys	Pro	Leu	Arg	Asp	Pro	Leu	Pro	Asp	Pro	Leu	Leu	Asp	Lys	Leu			
				165					170					175				
Val	Leu	Pro	Val	Leu	Pro	Gly	Ala	Leu	Gln	Ala	Arg	Pro	Gly	Pro	His			
				180					185					190				
Thr	Gln	Asp	Leu	Ser	Glu	Gln	Gln	Phe	Pro	Ile	Pro	Leu	Pro	Tyr	Cys			
				195					200					205				
Trp	Leu	Cys	Arg	Ala	Leu	Ile	Lys	Arg	Ile	Gln	Ala	Met	Ile	Pro	Lys			
				210					215					220				
Gly	Ala	Leu	Arg	Val	Ala	Val	Ala	Gln	Val	Cys	Arg	Val	Val	Pro	Leu			
225					230					235					240			
Val	Ala	Gly	Gly	Ile	Cys	Gln	Cys	Leu	Ala	Glu	Arg	Tyr	Ser	Val	Ile			
				245					250					255				
Leu	Leu	Asp	Thr	Leu	Leu	Gly	Arg	Met	Leu	Pro	Gln	Leu	Val	Cys	Arg			
				260					265					270				
Leu	Val	Leu	Arg	Cys	Ser	Met	Asp	Asp	Ser	Ala	Gly	Pro	Arg	Ser	Pro			
				275					280					285				
Thr	Gly	Glu	Trp	Leu	Pro	Arg	Asp	Ser	Glu	Cys	His	Leu	Cys	Met	Ser			
				290					295					300				
Val	Thr	Thr	Gln	Ala	Gly	Asn	Ser	Ser	Glu	Gln	Ala	Ile	Pro	Gln	Ala			
305					310					315					320			
Met	Leu	Gln	Ala	Cys	Val	Gly	Ser	Trp	Leu	Asp	Arg	Glu	Lys	Cys	Lys			
				325					330					335				
Gln	Phe	Val	Glu	Gln	His	Thr	Pro	Gln	Leu	Leu	Thr	Leu	Val	Pro	Arg			
				340					345					350				
Gly	Trp	Asp	Ala	His	Thr	Thr	Cys	Gln	Ala	Leu	Gly	Val	Cys	Gly	Thr			
				355					360					365				
Met	Ser	Ser	Pro	Leu	Gln	Cys	Ile	His	Ser	Pro	Asp	Leu						
				370					375					380				

<211> 379

<212> PRT

<213> Homo sapiens

<400> 26

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Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr
  1              5              10              15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys
          20              25              30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln
          35              40              45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly
          50              55              60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn
          65              70              75              80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu
          85              90              95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys
          100             105             110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln
          115             120             125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Leu Gly Cys Lys Ser
          130             135             140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro
          145             150             155             160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val
          165             170             175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr
          180             185             190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp
          195             200             205

Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly Ala
          210             215             220

Leu Arg Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu Val Ala
          225             230             235             240

Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu
          245             250             255

Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu Val
          260             265             270

Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly
          275             280             285

Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val Thr
          290             295             300

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Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met Leu  
305 310 315 320

Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe  
325 330 335

Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly Trp  
340 345 350

Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met Ser  
355 360 365

Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu  
370 375

<210> 27

<211> 527

<212> PRT

<213> Homo sapiens

<400> 27

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala  
1 5 10 15

Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp  
20 25 30

Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys  
35 40 45

Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp  
50 55 60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn  
65 70 75 80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp  
85 90 95

Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser  
100 105 110

Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro  
115 120 125

Gly Glu Val Cys Ser Ala Leu Asn Leu Cys Glu Ser Leu Gln Lys His  
130 135 140

Leu Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro  
145 150 155 160

Glu Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro  
165 170 175

Leu Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys  
180 185 190

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile  
195 200 205

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu  
 210 215 220  
 His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile  
 225 230 235 240  
 Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met  
 245 250 255  
 Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly  
 260 265 270  
 Phe Cys Asp Glu Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala  
 275 280 285  
 Lys Val Ala Ser Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro  
 290 295 300  
 Ile Lys Lys His Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val  
 305 310 315 320  
 Cys Glu Phe Leu Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys  
 325 330 335  
 Thr Glu Lys Glu Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu  
 340 345 350  
 Pro Lys Ser Leu Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly  
 355 360 365  
 Ser Ser Ile Leu Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val  
 370 375 380  
 Cys Ser Met Leu His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr  
 385 390 395 400  
 Val His Val Thr Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys  
 405 410 415  
 Lys Leu Val Gly Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys  
 420 425 430  
 Gln Glu Ile Leu Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp  
 435 440 445  
 Pro Tyr Gln Lys Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val  
 450 455 460  
 Leu Ile Glu Ile Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu  
 465 470 475 480  
 Lys Ile Gly Ala Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu  
 485 490 495  
 Lys Cys Ile Trp Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala  
 500 505 510  
 Ala Gln Cys Asn Ala Val Glu His Cys Lys Arg His Val Trp Asn  
 515 520 525

<210> 28  
 <211> 523  
 <212> PRT  
 <213> Homo sapiens

<400> 28  
 Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala  
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 Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp  
                   20                  25                  30  
 Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys  
                   35                  40                  45  
 Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp  
   50                  55                  60  
 Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn  
   65                  70                  75                  80  
 Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp  
                   85                  90                  95  
 Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser  
                   100                  105                  110  
 Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro  
   115                  120                  125  
 Gly Glu Val Cys Ser Ala Leu Leu Cys Glu Ser Leu Gln Lys His Leu  
   130                  135                  140  
 Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro Glu  
   145                  150                  155                  160  
 Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro Leu  
                   165                  170                  175  
 Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys Asp  
   180                  185                  190  
 Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln  
   195                  200                  205  
 Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His  
   210                  215                  220  
 Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys  
   225                  230                  235                  240  
 Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met  
                   245                  250                  255  
 His Met Gln Pro Lys Glu Ile Cys Ala Leu Val Gly Phe Cys Asp Glu  
                   260                  265                  270  
 Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala Lys Val Ala Ser  
   275                  280                  285



Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro Ile Lys Lys His  
 290 295 300  
 Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val Cys Glu Phe Leu  
 305 310 315 320  
 Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys Thr Glu Lys Glu  
 325 330 335  
 Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu Pro Lys Ser Leu  
 340 345 350  
 Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly Ser Ser Ile Leu  
 355 360 365  
 Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val Cys Ser Met Leu  
 370 375 380  
 His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr Val His Val Thr  
 385 390 395 400  
 Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys Lys Leu Val Gly  
 405 410 415  
 Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys Gln Glu Ile Leu  
 420 425 430  
 Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp Pro Tyr Gln Lys  
 435 440 445  
 Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val Leu Ile Glu Ile  
 450 455 460  
 Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu Lys Ile Gly Ala  
 465 470 475 480  
 Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu Lys Cys Ile Trp  
 485 490 495  
 Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala Ala Gln Cys Asn  
 500 505 510  
 Ala Val Glu His Cys Lys Arg His Val Trp Asn  
 515 520  
  
 <210> 29  
 <211> 380  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 29  
 Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr  
 1 5 10 15  
 Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys  
 20 25 30  
 Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln  
 35 40 45

Cys 50	Arg	Ala	Leu	Gly	His	Cys 55	Leu	Gln	Glu	Val	Trp 60	Gly	His	Val	Gly
Ala 65	Asp	Asp	Leu	Cys	Gln 70	Glu	Cys	Glu	Asp	Ile 75	Val	His	Ile	Leu	Asn 80
Lys	Met	Ala	Lys	Glu 85	Ala	Ile	Phe	Gln	Asp 90	Thr	Met	Arg	Lys	Phe 95	Leu
Glu	Gln	Glu	Cys 100	Asn	Val	Leu	Pro	Leu 105	Lys	Leu	Leu	Met	Pro 110	Gln	Cys
Asn	Gln	Val 115	Leu	Asp	Asp	Tyr	Phe 120	Pro	Leu	Val	Ile	Asp 125	Tyr	Phe	Gln
Asn 130	Gln	Thr	Asp	Ser	Asn	Gly 135	Ile	Cys	Met	His	Gly 140	Leu	Cys	Lys	Ser
Arg 145	Gln	Pro	Glu	Pro	Glu 150	Gln	Glu	Pro	Gly	Met 155	Ser	Asp	Pro	Leu	Pro 160
Lys	Pro	Leu	Arg	Asp 165	Pro	Leu	Pro	Asp	Pro 170	Leu	Leu	Asp	Lys	Leu 175	Val
Leu	Pro	Val	Leu 180	Pro	Gly	Ala	Leu	Gln 185	Ala	Arg	Pro	Gly	Pro 190	His	Thr
Gln	Asp	Leu 195	Ser	Glu	Gln	Gln	Phe 200	Pro	Ile	Pro	Leu	Pro 205	Tyr	Cys	Trp
Leu 210	Cys	Arg	Ala	Leu	Ile	Lys 215	Arg	Ile	Gln	Ala	Met 220	Ile	Pro	Lys	Gly
Ala 225	Leu	Ala	Val	Ala	Val 230	Ala	Gln	Val	Cys	Arg 235	Val	Val	Pro	Leu	Val 240
Ala	Gly	Gly	Ile	Cys 245	Gln	Cys	Leu	Ala	Glu 250	Arg	Tyr	Ser	Val	Ile 255	Leu
Leu	Asp	Thr	Leu 260	Leu	Gly	Arg	Met	Leu 265	Pro	Gln	Leu	Val	Cys 270	Arg	Leu
Val	Leu	Arg 275	Cys	Ser	Met	Asp	Asp 280	Ser	Ala	Gly	Pro	Arg 285	Ser	Pro	Thr
Gly 290	Glu	Trp	Leu	Pro	Arg	Asp 295	Ser	Glu	Cys	His 300	Leu	Cys	Met	Ser	Val
Thr 305	Thr	Gln	Ala	Gly	Asn 310	Ser	Ser	Glu	Gln	Ala 315	Ile	Pro	Gln	Ala	Met 320
Leu	Gln	Ala	Cys	Val 325	Gly	Ser	Trp	Leu	Asp 330	Arg	Glu	Lys	Cys	Lys 335	Gln
Phe	Val	Glu	Gln 340	His	Thr	Pro	Gln	Leu 345	Leu	Thr	Leu	Val	Pro 350	Arg	Gly
Trp	Asp	Ala 355	His	Thr	Thr	Cys	Gln 360	Ala	Leu	Gly	Val	Cys 365	Gly	Thr	Met
Ser	Ser	Pro	Leu	Gln	Cys	Ile	His	Ser	Pro	Asp	Leu				

370	375	380	
<p>&lt;210&gt; 30          &lt;211&gt; 4124          &lt;212&gt; DNA          &lt;213&gt; Homo sapiens</p>			
<p>&lt;400&gt; 30</p>			
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ctgtttccagc	caagcctggt	gctggacatg	gccaaaggtcc
ccggagaacc	tgtctgggcat	gcaggaagcc	atccagcagg
ctgagcatct	cagacccgca	gacgctggcc	agtgtgctga
ctgaacgatc	ctcgccctggt	catctcctat	gagcccagca
gtcccagcac	tcaccagcct	ctcagaagag	gaactgcttg
cgccatgagg	ttctggaggg	taatgtgggc	tacctgcggg
gaggtgctga	gcatgatggg	ggagttcctg	gtggcccacg
acctccgcct	tagtgctgga	tctccggcac	tgcacaggag
tacatcatct	cctacctgca	cccagggaac	accatcctgc
cgccccctcca	acaccaccac	ggagatctgg	accttgcccc
ggtgccgaca	aggatgtggt	ggtcctcacc	agcagccaga
atcgcgacaca	tccttaagca	gatgcgcagg	gccatcgctg
ggggccctgg	acctccggaa	gctgaggata	ggcgagtctg
gtgtccaggt	ccctggggcc	ccttggtgga	ggcagccaga
ctgccctgtg	tggggactcc	ggccgagcag	gccctggaga
ctgcgcagcg	cccttcacag	ggtagtccac	tgcctccagg
acgctggtgg	accgtgtgcc	caccctgctg	cagcacttgg
gtggtctccg	aggaagatct	ggtcaccaag	ctcaatgccg
gatcccaggc	tcctggtgcg	agccatcggg	cccacagaaa
gacgtgcag	ccgaagactc	accaggggtg	gccccagagt
cggcaagcac	tgggtggactc	tgtgttccag	gtgtcgggtg
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cctggagggc	catcctctgc	tgtgcccctg	ctcctgtcct
ggccccgtgc	acctcttcac	cacctatgat	cgcgcaccca
agccacatgg	agctcccggg	cccacgctac	agcacccaac
agccaccgca	ccgccacggc	cgcgaggagg	ttgccttcc
gcccacatgg	taggtgagat	caccgcgggc	aacctgctgc
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<213> Homo sapiens
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&lt;210&gt; 41

&lt;211&gt; 1043

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

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Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu  
 50 55 60

Asp Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe  
 65 70 75 80

Ile Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His  
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Glu Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu  
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Gly Thr Pro  
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## SEQUENCE LISTING

<110> BIOMERIEUX STELHYS

<120> Use of a polypeptide for detecting, preventing or treating  
a pathological condition associated with a degenerative,  
neurological or autoimmune disease

<130> SEP22

<140> PCT/FR00/02057

<141> 2000-07-17

<150> FR9909372

<151> 1999-07-15

<160> 75

<170> PatentIn Ver. 2.1

<210> 1

<211> 4393

<212> PRT

<213> Homo sapiens

<400> 1

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Gly Arg Leu Leu Ala Val Thr His Gly Leu Arg Ala Tyr Asp Gly Leu  
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Ser Leu Pro Glu Asp Ile Glu Thr Val Thr Ala Ser Gln Met Arg Trp  
35 40 45

Thr His Ser Tyr Leu Ser Asp Asp Glu Asp Met Leu Ala Asp Ser Ile  
50 55 60

Ser Gly Asp Asp Leu Gly Ser Gly Asp Leu Gly Ser Gly Asp Phe Gln  
65 70 75 80

Met Val Tyr Phe Arg Ala Leu Val Asn Phe Thr Arg Ser Ile Glu Tyr  
85 90 95

Ser Pro Gln Leu Glu Asp Ala Gly Ser Arg Glu Phe Arg Glu Val Ser  
100 105 110

Glu Ala Val Val Asp Thr Leu Glu Ser Glu Tyr Leu Lys Ile Pro Gly  
115 120 125

Asp Gln Val Val Ser Val Val Phe Ile Lys Glu Leu Asp Gly Trp Val  
130 135 140

Phe Val Glu Leu Asp Val Gly Ser Glu Gly Asn Ala Asp Gly Ala Gln  
145 150 155 160

Ile Gln Glu Met Leu Leu Arg Val Ile Ser Ser Gly Ser Val Ala Ser  
165 170 175

Tyr Val Thr Ser Pro Gln Gly Phe Gln Phe Arg Arg Leu Gly Thr Val  
180 185 190

Pro Gln Phe Pro Arg Ala Cys Thr Glu Ala Glu Phe Ala Cys His Ser  
195 200 205

Tyr Asn Glu Cys Val Ala Leu Glu Tyr Arg Cys Asp Arg Arg Pro Asp  
210 215 220

Cys Arg Asp Met Ser Asp Glu Leu Asn Cys Glu Glu Pro Val Leu Gly  
225 230 235 240

Ile Ser Pro Thr Phe Ser Leu Leu Val Glu Thr Thr Ser Leu Pro Pro  
245 250 255

Arg Pro Glu Thr Thr Ile Met Arg Gln Pro Pro Val Thr His Ala Pro  
260 265 270

Gln Pro Leu Leu Pro Gly Ser Val Arg Pro Leu Pro Cys Gly Pro Gln  
275 280 285

Glu Ala Ala Cys Arg Asn Gly His Cys Ile Pro Arg Asp Tyr Leu Cys  
290 295 300

Asp Gly Gln Glu Asp Cys Glu Asp Gly Ser Asp Glu Leu Asp Cys Gly  
305 310 315 320

Pro Pro Pro Pro Cys Glu Pro Asn Glu Phe Pro Cys Gly Asn Gly His  
325 330 335

Cys Ala Leu Lys Leu Trp Arg Cys Asp Gly Asp Phe Asp Cys Glu Asp  
340 345 350

Arg Thr Asp Glu Ala Asn Cys Pro Thr Lys Arg Pro Glu Glu Val Cys  
355 360 365

Gly Pro Thr Gln Phe Arg Cys Val Ser Thr Asn Met Cys Ile Pro Ala  
370 375 380

Ser Phe His Cys Asp Glu Glu Ser Asp Cys Pro Asp Arg Ser Asp Glu  
385 390 395 400

Phe Gly Cys Met Pro Pro Gln Val Val Thr Pro Pro Arg Glu Ser Ile  
405 410 415

Gln Ala Ser Arg Gly Gln Thr Val Thr Phe Thr Cys Val Ala Ile Gly  
420 425 430

Val Pro Ala Pro Phe Leu Ile Asn Trp Arg Leu Asn Trp Gly His Ile  
435 440 445

Pro Ser Gln Pro Arg Val Thr Val Thr Ser Glu Gly Gly Arg Gly Thr

450	455	460	
Leu Ile Ile Arg Asp Val Lys Glu Ser Asp Gln Gly Ala Tyr Thr Cys			
465	470	475	480
Glu Ala Met Asn Ala Arg Gly Met Val Phe Gly Ile Pro Asp Gly Val			
	485	490	495
Leu Glu Leu Val Pro Gln Arg Ala Gly Pro Cys Pro Asp Gly His Phe			
	500	505	510
Tyr Leu Glu His Ser Ala Ala Cys Leu Pro Cys Phe Cys Phe Gly Ile			
	515	520	525
Thr Ser Val Cys Gln Ser Thr Arg Arg Phe Arg Asp Gln Ile Arg Leu			
	530	535	540
Arg Phe Asp Gln Pro Asp Asp Phe Lys Gly Val Asn Val Thr Met Pro			
545	550	555	560
Ala Gln Pro Gly Thr Pro Pro Leu Ser Ser Thr Gln Leu Gln Ile Asp			
	565	570	575
Pro Ser Leu His Glu Phe Gln Leu Val Asp Leu Ser Arg Arg Phe Leu			
	580	585	590
Val His Asp Ser Phe Trp Ala Leu Pro Glu Gln Phe Leu Gly Asn Lys			
	595	600	605
Val Asp Ser Tyr Gly Gly Ser Leu Arg Tyr Asn Val Arg Tyr Glu Leu			
	610	615	620
Ala Arg Gly Met Leu Glu Pro Val Gln Arg Pro Asp Val Val Leu Val			
625	630	635	640
Gly Ala Gly Tyr Arg Leu Leu Ser Arg Gly His Thr Pro Thr Gln Pro			
	645	650	655

Gly Ala Leu Asn Gln Arg Gln Val Gln Phe Ser Glu Glu His Trp Val  
660 665 670

His Glu Ser Gly Arg Pro Val Gln Arg Ala Glu Leu Leu Gln Val Leu  
675 680 685

Gln Ser Leu Glu Ala Val Leu Ile Gln Thr Val Tyr Asn Thr Lys Met  
690 695 700

Ala Ser Val Gly Leu Ser Asp Ile Ala Met Asp Thr Thr Val Thr His  
705 710 715 720

Ala Thr Ser His Gly Arg Ala His Ser Val Glu Glu Cys Arg Cys Pro  
725 730 735

Ile Gly Tyr Ser Gly Leu Ser Cys Glu Ser Cys Asp Ala His Phe Thr  
740 745 750

Arg Val Pro Gly Gly Pro Tyr Leu Gly Thr Cys Ser Gly Cys Ser Cys  
755 760 765

Asn Gly His Ala Ser Ser Cys Asp Pro Val Tyr Gly His Cys Leu Asn  
770 775 780

Cys Gln His Asn Thr Glu Gly Pro Gln Cys Lys Lys Cys Lys Ala Gly  
785 790 795 800

Phe Phe Gly Asp Ala Met Lys Ala Thr Ala Thr Ser Cys Arg Pro Cys  
805 810 815

Pro Cys Pro Tyr Ile Asp Ala Ser Arg Arg Phe Ser Asp Thr Cys Phe  
820 825 830

Leu Asp Thr Asp Gly Gln Ala Thr Cys Asp Ala Cys Ala Pro Gly Tyr  
835 840 845

Thr Gly Arg Arg Cys Glu Ser Cys Ala Pro Gly Tyr Glu Gly Asn Pro  
850 855 860

Ile Gln Pro Gly Gly Lys Cys Arg Pro Val Asn Gln Glu Ile Val Arg  
865 870 875 880

Cys Asp Glu Arg Gly Ser Met Gly Thr Ser Gly Glu Ala Cys Arg Cys  
885 890 895

Lys Asn Asn Val Val Gly Arg Leu Cys Asn Glu Cys Ala Asp Arg Ser  
900 905 910

Phe His Leu Ser Thr Arg Asn Pro Asp Gly Cys Leu Lys Cys Phe Cys  
915 920 925

Met Gly Val Ser Arg His Cys Thr Ser Ser Ser Trp Ser Arg Ala Gln  
930 935 940

Leu His Gly Ala Ser Glu Glu Pro Gly His Phe Ser Leu Thr Asn Ala  
945 950 955 960

Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe Ser Pro Thr Pro Gly  
965 970 975

Glu Leu Gly Phe Ser Ser Phe His Arg Leu Leu Ser Gly Pro Tyr Phe  
980 985 990

Trp Ser Leu Pro Ser Arg Phe Leu Gly Asp Lys Val Thr Ser Tyr Gly  
995 1000 1005

Gly Glu Leu Arg Phe Thr Val Thr Gln Arg Ser Gln Pro Gly Ser Thr  
1010 1015 1020

Pro Leu His Gly Gln Pro Leu Val Val Leu Gln Gly Asn Asn Ile Ile  
1025 1030 1035 1040

Leu Glu His His Val Ala Gln Glu Pro Ser Pro Gly Gln Pro Ser Thr

	1045		1050		1055
Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln Arg Pro Asp Gly Gln					
	1060		1065		1070
Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu Ala Gly Ile Asp Thr					
	1075		1080		1085
Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro Ala Glu Ser Arg Val					
	1090		1095		1100
Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu Glu Thr Gly Gln Asp					
1105		1110		1115	1120
Pro Ala Leu Glu Val Glu Gln Cys Ser Cys Pro Pro Gly Tyr Arg Gly					
	1125		1130		1135
Pro Ser Cys Gln Asp Cys Asp Thr Gly Tyr Thr Arg Thr Pro Ser Gly					
	1140		1145		1150
Leu Tyr Leu Gly Thr Cys Glu Arg Cys Ser Cys His Gly His Ser Glu					
	1155		1160		1165
Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly Cys Gln His His Thr					
	1170		1175		1180
Glu Gly Pro Arg Cys Glu Gln Cys Gln Pro Gly Tyr Tyr Gly Asp Ala					
1185		1190		1195	1200
Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys Pro Cys Tyr Gly Asp					
	1205		1210		1215
Pro Ala Ala Gly Gln Ala Ala His Thr Cys Phe Leu Asp Thr Asp Gly					
	1220		1225		1230
His Pro Thr Cys Asp Ala Cys Ser Pro Gly His Ser Gly Arg His Cys					
	1235		1240		1245



Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn Pro Ser Gln Gly Gln Pro  
 1250 1255 1260

Cys Gln Arg Asp Ser Gln Val Pro Gly Pro Ile Gly Cys Asn Cys Asp  
 1265 1270 1275 1280

Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala Ala Gly Gln Cys Gln  
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Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser His Cys Arg Pro His  
 1300 1305 1310

His Phe His Leu Ser Ala Ser Asn Pro Asp Gly Cys Leu Pro Cys Phe  
 1315 1320 1325

Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser Ala Tyr Thr Arg His  
 1330 1335 1340

Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe Gln Gly Phe Ala Leu  
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Val Asn Pro Gln Arg Asn Ser Arg Leu Thr Gly Glu Phe Thr Val Glu  
 1365 1370 1375

Pro Val Pro Glu Gly Ala Gln Leu Ser Phe Gly Asn Phe Ala Gln Leu  
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Gly His Glu Ser Phe Tyr Trp Gln Leu Pro Glu Thr Tyr Gln Gly Asp  
 1395 1400 1405

Lys Val Ala Ala Tyr Gly Gly Lys Leu Arg Tyr Thr Leu Ser Tyr Thr  
 1410 1415 1420

Ala Gly Pro Gln Gly Ser Pro Leu Ser Asp Pro Asp Val Gln Ile Thr  
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Gly Asn Asn Ile Met Leu Val Ala Ser Gln Pro Ala Leu Gln Gly Pro  
 1445 1450 1455

Glu Arg Arg Ser Tyr Glu Ile Met Phe Arg Glu Glu Phe Trp Arg Arg  
 1460 1465 1470

Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu Ala  
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Asp Leu Asp Glu Leu Leu Ile Arg Ala Thr Phe Ser Ser Val Pro Leu  
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Val Ala Ser Ile Ser Ala Val Ser Leu Glu Val Ala Gln Pro Gly Pro  
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Ser Asn Arg Pro Arg Ala Leu Glu Val Glu Glu Cys Arg Cys Pro Pro  
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Gly Tyr Ile Gly Leu Ser Cys Gln Asp Cys Ala Pro Gly Tyr Thr Arg  
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Thr Gly Ser Gly Leu Tyr Leu Gly His Cys Glu Leu Cys Glu Cys Asn  
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Gly His Ser Asp Leu Cys His Pro Glu Thr Gly Ala Cys Ser Gln Cys  
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Gln His Asn Ala Ala Gly Glu Phe Cys Glu Leu Cys Ala Pro Gly Tyr  
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Tyr Gly Asp Ala Thr Ala Gly Thr Pro Glu Asp Cys Gln Pro Cys Ala  
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Cys Pro Leu Thr Asn Pro Glu Asn Met Phe Ser Arg Thr Cys Glu Ser  
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Leu Gly Ala Gly Gly Tyr Arg Cys Thr Ala Cys Glu Pro Gly Tyr Thr

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Gly Gln Tyr Cys Glu Gln Cys Gly Pro Gly Tyr Val Gly Asn Pro Ser			
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Val Gln Gly Gly Gln Cys Leu Pro Glu Thr Asn Gln Ala Pro Leu Val			
1665	1670	1675	1680
Val Glu Val His Pro Ala Arg Ser Ile Val Pro Gln Gly Gly Ser His			
	1685	1690	1695
Ser Leu Arg Cys Gln Val Ser Gly Arg Gly Pro His Tyr Phe Tyr Trp			
	1700	1705	1710
Ser Arg Glu Asp Gly Arg Pro Val Pro Ser Gly Thr Gln Gln Arg His			
	1715	1720	1725
Gln Gly Ser Glu Leu His Phe Pro Ser Val Gln Pro Ser Asp Ala Gly			
	1730	1735	1740
Val Tyr Ile Cys Thr Cys Arg Asn Leu His Arg Ser Asn Thr Ser Arg			
1745	1750	1755	1760
Ala Glu Leu Leu Val Thr Glu Ala Pro Ser Lys Pro Ile Thr Val Thr			
	1765	1770	1775
Val Glu Glu Gln Arg Ser Gln Ser Val Arg Pro Gly Ala Asp Val Thr			
	1780	1785	1790
Phe Ile Cys Thr Ala Lys Ser Lys Ser Pro Ala Tyr Thr Leu Val Trp			
	1795	1800	1805
Thr Arg Leu His Asn Gly Lys Leu Pro Thr Arg Ala Met Asp Phe Asn			
1810	1815	1820	
Gly Ile Leu Thr Ile Arg Asn Val Gln Leu Ser Asp Ala Gly Thr Tyr			
1825	1830	1835	1840

Ile Thr Thr Ala Asp Ala Gly Phe Tyr Leu Cys Val Ala Thr Ser Pro  
2020 2025 2030

Ala Gly Thr Ala Gln Ala Arg Ile Gln Val Val Val Leu Ser Ala Ser  
2035 2040 2045

Asp Ala Ser Gln Pro Pro Val Lys Ile Glu Ser Ser Ser Pro Ser Val  
2050 2055 2060

Thr Glu Gly Gln Thr Leu Asp Leu Asn Cys Val Val Ala Gly Ser Ala  
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His Ala Gln Val Thr Trp Tyr Arg Arg Gly Gly Ser Leu Pro His His  
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Thr Gln Val His Gly Ser Arg Leu Arg Leu Pro Gln Val Ser Pro Ala  
2100 2105 2110

Asp Ser Gly Glu Tyr Val Cys Arg Val Glu Asn Gly Ser Gly Pro Lys  
2115 2120 2125

Glu Ala Ser Ile Thr Val Ser Val Leu His Gly Thr His Ser Gly Pro  
2130 2135 2140

Ser Tyr Thr Pro Val Pro Gly Ser Thr Arg Pro Ile Arg Ile Glu Pro  
2145 2150 2155 2160

Ser Ser Ser His Val Ala Glu Gly Gln Thr Leu Asp Leu Asn Cys Val  
2165 2170 2175

Val Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly  
2180 2185 2190

Ser Leu Pro Ala Arg His Gln Thr His Gly Ser Leu Leu Arg Leu His  
2195 2200 2205

Gln Val Thr Pro Ala Asp Ser Gly Glu Tyr Val Cys His Val Val Gly  
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Thr Ser Gly Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Ala Ser

2225                      2230                      2235                      2240

Val Ile Pro Gly Pro Ile Pro Pro Val Arg Ile Glu Ser Ser Ser Ser

2245                      2250                      2255

Thr Val Ala Glu Gly Gln Thr Leu Asp Leu Ser Cys Val Val Ala Gly

2260                      2265                      2270

Gln Ala His Ala Gln Val Thr Trp Tyr Lys Arg Gly Gly Ser Leu Pro

2275                      2280                      2285

Ala Arg His Gln Val Arg Gly Ser Arg Leu Tyr Ile Phe Gln Ala Ser

2290                      2295                      2300

Pro Ala Asp Ala Gly Gln Tyr Val Cys Arg Ala Ser Asn Gly Met Glu

2305                      2310                      2315                      2320

Ala Ser Ile Thr Val Thr Val Thr Gly Thr Gln Gly Ala Asn Leu Ala

2325                      2330                      2335

Tyr Pro Ala Gly Ser Thr Gln Pro Ile Arg Ile Glu Pro Ser Ser Ser

2340                      2345                      2350

Gln Val Ala Glu Gly Gln Thr Leu Asp Leu Asn Cys Val Val Pro Gly

2355                      2360                      2365

Gln Ser His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser Leu Pro

2370                      2375                      2380

Val Arg His Gln Thr His Gly Ser Leu Leu Arg Leu Tyr Gln Ala Ser

2385                      2390                      2395                      2400

Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Leu Gly Ser Ser Val

2405                      2410                      2415

Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Pro Ala Gly Ser Val

2420                      2425                      2430

Pro Ala Leu Gly Val Thr Pro Thr Val Arg Ile Glu Ser Ser Ser Ser

2435

2440

2445

Gln Val Ala Glu Gly Gln Thr Leu Asp Leu Asn Cys Leu Val Ala Gly

2450

2455

2460

Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser Leu Pro

2465

2470

2475

2480

Ala Arg His Gln Val His Gly Ser Arg Leu Arg Leu Leu Gln Val Thr

2485

2490

2495

Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Val Gly Ser Ser Gly

2500

2505

2510

Thr Gln Glu Ala Ser Val Leu Val Thr Ile Gln Gln Arg Leu Ser Gly

2515

2520

2525

Ser His Ser Gln Gly Val Ala Tyr Pro Val Arg Ile Glu Ser Ser Ser

2530

2535

2540

Ala Ser Leu Ala Asn Gly His Thr Leu Asp Leu Asn Cys Leu Val Ala

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2550

2555

2560

Ser Gln Ala Pro His Thr Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu

2565

2570

2575

Pro Ser Arg His Gln Ile Val Gly Ser Arg Leu Arg Ile Pro Gln Val

2580

2585

2590

Thr Pro Ala Asp Ser Gly Glu Tyr Val Cys His Val Ser Asn Gly Ala

2595

2600

2605

Gly Ser Arg Glu Thr Ser Leu Ile Val Thr Ile Gln Gly Ser Gly Ser

2610

2615

2620

Ser His Val Pro Arg Val Ser Pro Pro Ile Arg Ile Glu Ser Ser Ser  
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Pro Thr Val Val Glu Gly Gln Thr Leu Asp Leu Asn Cys Val Val Ala  
2645 2650 2655

Arg Gln Pro Gln Ala Ile Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu  
2660 2665 2670

Pro Ser Arg His Gln Thr His Gly Ser His Leu Arg Leu His Gln Met  
2675 2680 2685

Ser Val Ala Asp Ser Gly Glu Tyr Val Cys Arg Ala Asn Asn Asn Ile  
2690 2695 2700

Asp Ala Leu Glu Ala Ser Ile Val Ile Ser Val Ser Pro Ser Ala Gly  
2705 2710 2715 2720

Ser Pro Ser Ala Pro Gly Ser Ser Met Pro Ile Arg Ile Glu Ser Ser  
2725 2730 2735

Ser Ser His Val Ala Glu Gly Glu Thr Leu Asp Leu Asn Cys Val Val  
2740 2745 2750

Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser  
2755 2760 2765

Leu Pro Ser Tyr His Gln Thr Arg Gly Ser Arg Leu Arg Leu His His  
2770 2775 2780

Val Ser Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Met Gly Ser  
2785 2790 2795 2800

Ser Gly Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Ala Ser Gly  
2805 2810 2815

Ser Ser Ala Val His Val Pro Ala Pro Gly Gly Ala Pro Pro Ile Arg



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Ile Glu Pro Ser Ser Ser Arg Val Ala Glu Gly Gln Thr Leu Asp Leu			
2835	2840	2845	
Lys Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys			
2850	2855	2860	
Arg Gly Gly Asn Leu Pro Ala Arg His Gln Val His Gly Pro Leu Leu			
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Arg Leu Asn Gln Val Ser Pro Ala Asp Ser Gly Glu Tyr Ser Cys Gln			
2885	2890	2895	
Val Thr Gly Ser Ser Gly Thr Leu Glu Ala Ser Val Leu Val Thr Ile			
2900	2905	2910	
Glu Pro Ser Ser Pro Gly Pro Ile Pro Ala Pro Gly Leu Ala Gln Pro			
2915	2920	2925	
Ile Tyr Ile Glu Ala Ser Ser Ser His Val Thr Glu Gly Gln Thr Leu			
2930	2935	2940	
Asp Leu Asn Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp			
2945	2950	2955	2960
Tyr Lys Arg Gly Gly Ser Leu Pro Ala Arg His Gln Thr His Gly Ser			
2965	2970	2975	
Gln Leu Arg Leu His His Val Ser Pro Ala Asp Ser Gly Glu Tyr Val			
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Cys Arg Ala Ala Gly Gly Pro Gly Pro Glu Gln Glu Ala Ser Phe Thr			
2995	3000	3005	
Val Thr Val Pro Pro Ser Glu Gly Ser Ser Tyr Arg Leu Arg Ser Pro			
3010	3015	3020	

Val Ile Ser Ile Asp Pro Pro Ser Ser Thr Val Gln Gln Gly Gln Asp  
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Ala Ser Phe Lys Cys Leu Ile His Asp Gly Ala Ala Pro Ile Ser Leu  
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Glu Trp Lys Thr Arg Asn Gln Glu Leu Glu Asp Asn Val His Ile Ser  
 3060 3065 3070

Pro Asn Gly Ser Ile Ile Thr Ile Val Gly Thr Arg Pro Ser Asn His  
 3075 3080 3085

Gly Thr Tyr Arg Cys Val Ala Ser Asn Ala Tyr Gly Val Ala Gln Ser  
 3090 3095 3100

Val Val Asn Leu Ser Val His Gly Pro Pro Thr Val Ser Val Leu Pro  
 3105 3110 3115 3120

Glu Gly Pro Val Trp Val Lys Val Gly Lys Ala Val Thr Leu Glu Cys  
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Val Ser Ala Gly Glu Pro Arg Ser Ser Ala Arg Trp Thr Arg Ile Ser  
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Ser Thr Pro Ala Lys Leu Glu Gln Arg Thr Tyr Gly Leu Met Asp Ser  
 3155 3160 3165

His Thr Val Leu Gln Ile Ser Ser Ala Lys Pro Ser Asp Ala Gly Thr  
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Tyr Val Cys Leu Ala Gln Asn Ala Leu Gly Thr Ala Gln Lys Gln Val  
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Glu Val Ile Val Asp Thr Gly Ala Met Ala Pro Gly Ala Pro Gln Val  
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Gln Ala Glu Glu Ala Glu Leu Thr Val Glu Ala Gly His Thr Ala Thr

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3225

3230

Leu Arg Cys Ser Ala Thr Gly Ser Pro Ala Arg Thr Ile His Trp Ser

3235

3240

3245

Lys Leu Arg Ser Pro Leu Pro Trp Gln His Arg Leu Glu Gly Asp Thr

3250

3255

3260

Leu Ile Ile Pro Arg Val Ala Gln Gln Asp Ser Gly Gln Tyr Ile Cys

3265

3270

3275

3280

Asn Ala Thr Ser Pro Ala Gly His Ala Glu Ala Thr Ile Ile Leu His

3285

3290

3295

Val Glu Ser Pro Pro Tyr Ala Thr Thr Val Pro Glu His Ala Ser Val

3300

3305

3310

Gln Ala Gly Glu Thr Val Gln Leu Gln Cys Leu Ala His Gly Thr Pro

3315

3320

3325

Pro Leu Thr Phe Gln Trp Ser Arg Val Gly Ser Ser Leu Pro Gly Arg

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3335

3340

Ala Thr Ala Arg Asn Glu Leu Leu His Phe Glu Arg Ala Ala Pro Glu

3345

3350

3355

3360

Asp Ser Gly Arg Tyr Arg Cys Arg Val Thr Asn Lys Val Gly Ser Ala

3365

3370

3375

Glu Ala Phe Ala Gln Leu Leu Val Gln Gly Pro Pro Gly Ser Leu Pro

3380

3385

3390

Ala Thr Ser Ile Pro Ala Gly Ser Thr Pro Thr Val Gln Val Thr Pro

3395

3400

3405

Gln Leu Glu Thr Lys Ser Ile Gly Ala Ser Val Glu Phe His Cys Ala

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Val Pro Ser Asp Arg Gly Thr Gln Leu Arg Trp Phe Lys Glu Gly Gly			
3425	3430	3435	3440
Gln Leu Pro Pro Gly His Ser Val Gln Asp Gly Val Leu Arg Ile Gln			
	3445	3450	3455
Asn Leu Asp Gln Ser Cys Gln Gly Thr Tyr Ile Cys Gln Ala His Gly			
	3460	3465	3470
Pro Trp Gly Lys Ala Gln Ala Ser Ala Gln Leu Val Ile Gln Ala Leu			
	3475	3480	3485
Pro Ser Val Leu Ile Asn Ile Arg Thr Ser Val Gln Thr Val Val Val			
	3490	3495	3500
Gly His Ala Val Glu Phe Glu Cys Leu Ala Leu Gly Asp Pro Lys Pro			
3505	3510	3515	3520
Gln Val Thr Trp Ser Lys Val Gly Gly His Leu Arg Pro Gly Ile Val			
	3525	3530	3535
Gln Ser Gly Gly Val Val Arg Ile Ala His Val Glu Leu Ala Asp Ala			
	3540	3545	3550
Gly Gln Tyr Arg Cys Thr Ala Thr Asn Ala Ala Gly Thr Thr Gln Ser			
	3555	3560	3565
His Val Leu Leu Leu Val Gln Ala Leu Pro Gln Ile Ser Met Pro Gln			
	3570	3575	3580
Glu Val Arg Val Pro Ala Gly Ser Ala Ala Val Phe Pro Cys Ile Ala			
3585	3590	3595	3600
Ser Gly Tyr Pro Thr Pro Asp Ile Ser Trp Ser Lys Leu Asp Gly Ser			
	3605	3610	3615

Leu Pro Pro Asp Ser Arg Leu Glu Asn Asn Met Leu Met Leu Pro Ser  
 3620 3625 3630

Val Gln Pro Gln Asp Ala Gly Thr Tyr Val Cys Thr Ala Thr Asn Arg  
 3635 3640 3645

Gln Gly Lys Val Lys Ala Phe Ala His Leu Gln Val Pro Glu Arg Val  
 3650 3655 3660

Val Pro Tyr Phe Thr Gln Thr Pro Tyr Ser Phe Leu Pro Leu Pro Thr  
 3665 3670 3675 3680

Ile Lys Asp Ala Tyr Arg Lys Phe Glu Ile Lys Ile Thr Phe Arg Pro  
 3685 3690 3695

Asp Ser Ala Asp Gly Met Leu Leu Tyr Asn Gly Gln Lys Arg Val Pro  
 3700 3705 3710

Gly Ser Pro Thr Asn Leu Ala Asn Arg Gln Pro Asp Phe Ile Ser Phe  
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Gly Leu Val Gly Gly Arg Pro Glu Phe Arg Phe Asp Ala Gly Ser Gly  
 3730 3735 3740

Met Ala Thr Ile Arg His Pro Thr Pro Leu Ala Leu Gly His Phe His  
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Thr Val Thr Leu Leu Arg Ser Leu Thr Gln Gly Ser Leu Ile Val Gly  
 3765 3770 3775

Asp Leu Ala Pro Val Asn Gly Thr Ser Gln Gly Lys Phe Gln Gly Leu  
 3780 3785 3790

Asp Leu Asn Glu Glu Leu Tyr Leu Gly Gly Tyr Pro Asp Tyr Gly Ala  
 3795 3800 3805

Ile Pro Lys Ala Gly Leu Ser Ser Gly Phe Ile Gly Cys Val Arg Glu  
 3810 3815 3820

Leu Arg Ile Gln Gly Glu Glu Ile Val Phe His Asp Leu Asn Leu Thr  
 3825 3830 3835 3840

Ala His Gly Ile Ser His Cys Pro Thr Cys Arg Asp Arg Pro Cys Gln  
 3845 3850 3855

Asn Gly Gly Gln Cys His Asp Ser Glu Ser Ser Ser Tyr Val Cys Val  
 3860 3865 3870

Cys Pro Ala Gly Phe Thr Gly Ser Arg Cys Glu His Ser Gln Ala Leu  
 3875 3880 3885

His Cys His Pro Glu Ala Cys Gly Pro Asp Ala Thr Cys Val Asn Arg  
 3890 3895 3900

Pro Asp Gly Arg Gly Tyr Thr Cys Arg Cys His Leu Gly Arg Ser Gly  
 3905 3910 3915 3920

Leu Arg Cys Glu Glu Gly Val Thr Val Thr Thr Pro Ser Leu Ser Gly  
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Ala Gly Ser Tyr Leu Ala Leu Pro Ala Leu Thr Asn Thr His His Glu  
 3940 3945 3950

Leu Arg Leu Asp Val Glu Phe Lys Pro Leu Ala Pro Asp Gly Val Leu  
 3955 3960 3965

Leu Phe Ser Gly Gly Lys Ser Gly Pro Val Glu Asp Phe Val Ser Leu  
 3970 3975 3980

Ala Met Val Gly Gly His Leu Glu Phe Arg Tyr Glu Leu Gly Ser Gly  
 3985 3990 3995 4000

Leu Ala Val Leu Arg Thr Ala Glu Pro Leu Ala Leu Gly Arg Trp His

4005	4010	4015	
Arg Val Ser Ala Glu Arg Leu Asn Lys Asp Gly Ser Leu Arg Val Asn			
4020	4025	4030	
Gly Gly Arg Pro Val Leu Arg Ser Ser Pro Gly Lys Ser Gln Gly Leu			
4035	4040	4045	
Asn Leu His Thr Leu Leu Tyr Leu Gly Gly Val Glu Pro Ser Val Pro			
4050	4055	4060	
Leu Ser Pro Ala Thr Asn Met Ser Ala His Phe Arg Gly Cys Val Gly			
4065	4070	4075	4080
Glu Val Ser Val Asn Gly Lys Arg Leu Asp Leu Thr Tyr Ser Phe Leu			
4085	4090	4095	
Gly Ser Gln Gly Ile Gly Gln Cys Tyr Asp Ser Ser Pro Cys Glu Arg			
4100	4105	4110	
Gln Pro Cys Gln His Gly Ala Thr Cys Met Pro Ala Gly Glu Tyr Glu			
4115	4120	4125	
Phe Gln Cys Leu Cys Arg Asp Gly Ile Lys Gly Asp Leu Cys Glu His			
4130	4135	4140	
Glu Glu Asn Pro Cys Gln Leu Arg Glu Pro Cys Leu His Gly Gly Thr			
4145	4150	4155	4160
Cys Gln Gly Thr Arg Cys Leu Cys Leu Pro Gly Phe Ser Gly Pro Arg			
4165	4170	4175	
Cys Gln Gln Gly Ser Gly His Gly Ile Ala Glu Ser Asp Trp His Leu			
4180	4185	4190	
Glu Gly Ser Gly Gly Asn Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe			
4195	4200	4205	

His Asp Asp Gly Phe Leu Ala Phe Pro Gly His Val Phe Ser Arg Ser

4210

4215

4220

Leu Pro Glu Val Pro Glu Thr Ile Glu Leu Glu Val Arg Thr Ser Thr

4225

4230

4235

4240

Ala Ser Gly Leu Leu Leu Trp Gln Gly Val Glu Val Gly Glu Ala Gly

4245

4250

4255

Gln Gly Lys Asp Phe Ile Ser Leu Gly Leu Gln Asp Gly His Leu Val

4260

4265

4270

Phe Arg Tyr Gln Leu Gly Ser Gly Glu Ala Arg Leu Val Ser Glu Asp

4275

4280

4285

Pro Ile Asn Asp Gly Glu Trp His Arg Val Thr Ala Leu Arg Glu Gly

4290

4295

4300

Arg Arg Gly Ser Ile Gln Val Asp Gly Glu Glu Leu Val Ser Gly Arg

4305

4310

4315

4320

Ser Pro Gly Pro Asn Val Ala Val Asn Ala Lys Gly Ser Ile Tyr Ile

4325

4330

4335

Gly Gly Ala Pro Asp Val Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser

4340

4345

4350

Gly Ile Thr Gly Cys Val Lys Asn Leu Val Leu His Ser Ala Arg Pro

4355

4360

4365

Gly Ala Pro Pro Pro Gln Pro Leu Asp Leu Gln His Arg Ala Gln Ala

4370

4375

4380

Gly Ala Asn Thr Arg Pro Cys Pro Ser

4385

4390



&lt;210&gt; 2

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 2

Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe His Asp Asp Gly Phe Leu  
 1 5 10 15

Ala Phe Pro Gly His Val Phe Ser Arg Ser Leu Pro Glu Val Pro Glu  
 20 25 30

Thr Ile Glu Leu Glu Val Arg Thr Ser Thr Ala Ser Gly Leu Leu Leu  
 35 40 45

Trp Gln Gly Val Glu Val Gly Glu Ala Gly Gln Gly Lys Asp Phe Ile  
 50 55 60

Ser Leu Gly Leu Gln Asp Gly His Leu Val Phe Arg Tyr Gln Leu Gly  
 65 70 75 80

Ser Gly Glu Ala Arg Leu Val Ser Glu Asp Pro Ile Asn Asp Gly Glu  
 85 90 95

Trp His Arg Val Thr Ala Leu Arg Glu Gly Arg Arg Gly Ser Ile Gln  
 100 105 110

Val Asp Gly Glu Glu Leu Val Ser Gly Arg Ser Pro Gly Pro Asn Val  
 115 120 125

Ala Val Asn Ala Lys Gly Ser Val Tyr Ile Gly Gly Ala Pro Asp Val  
 130 135 140

Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser Gly Ile Thr Gly Cys Val  
 145 150 155 160

Lys Asn Leu Val Leu His Ser Ala Arg Pro Gly Ala Pro Pro Pro Gln  
165 170 175

Pro Leu Asp Leu Gln His Arg Ala Gln Ala Gly Ala Asn Thr Arg Pro  
180 185 190

Cys Pro Ser  
195

<210> 3

<211> 508

<212> PRT

<213> Homo sapiens

<400> 3

Arg Thr Cys Arg Cys Lys Asn Asn Val Val Gly Arg Leu Cys Asn Glu  
1 5 10 15

Cys Ala Asp Arg Ser Phe His Leu Ser Thr Arg Asn Pro Asp Gly Cys  
20 25 30

Leu Lys Cys Phe Cys Met Gly Val Ser Arg His Cys Thr Ser Ser Ser  
35 40 45

Trp Ser Arg Ala Gln Leu His Gly Ala Ser Glu Glu Pro Gly His Phe  
50 55 60

Ser Leu Thr Asn Ala Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe  
65 70 75 80

Ser Pro Thr Pro Gly Glu Leu Gly Phe Ser Ser Phe His Arg Leu Leu  
85 90 95

Ser Gly Pro Tyr Phe Trp Ser Leu Pro Ser Arg Phe Leu Gly Asp Lys

100	105	110	
Val Thr Ser Tyr Gly Gly Glu Leu Arg Phe Thr Val Thr Gln Arg Ser			
115	120	125	
Gln Pro Gly Ser Thr Pro Leu His Gly Gln Pro Leu Val Val Leu Gln			
130	135	140	
Gly Asn Asn Ile Ile Leu Glu His His Val Ala Gln Glu Pro Ser Pro			
145	150	155	160
Gly Gln Pro Ser Thr Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln			
165	170	175	
Arg Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu			
180	185	190	
Ala Gly Ile Asp Thr Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro			
195	200	205	
Ala Glu Ser Arg Leu Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu			
210	215	220	
Glu Thr Gly Gln Asp Pro Ala Leu Glu Val Glu Gln Cys Ser Cys Pro			
225	230	235	240
Pro Gly Tyr Leu Gly Pro Ser Cys Gln Asp Cys Asp Thr Gly Tyr Thr			
245	250	255	
Arg Thr Pro Ser Gly Leu Tyr Leu Gly Thr Cys Glu Arg Cys Ser Cys			
260	265	270	
His Gly His Ser Glu Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly			
275	280	285	
Cys Gln His His Thr Glu Gly Pro Arg Cys Glu Gln Cys Gln Pro Gly			
290	295	300	

Tyr Tyr Gly Asp Ala Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys

305 310 315 320

Pro Cys Tyr Gly Asp Pro Ala Ala Gly Gln Ala Ala Leu Thr Cys Phe

325 330 335

Leu Asp Thr Asp Gly His Pro Thr Cys Asp Ala Cys Ser Pro Gly His

340 345 350

Ser Gly Arg His Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn Pro

355 360 365

Ser Gln Gly Gln Pro Cys Gln Arg Asp Ser Gln Val Pro Gly Pro Ile

370 375 380

Gly Cys Asn Cys Asp Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala

385 390 395 400

Ala Gly Gln Cys Gln Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser

405 410 415

His Cys Arg Pro His His Phe His Leu Ser Ala Ser Asn Pro Asp Gly

420 425 430

Cys Leu Pro Cys Phe Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser

435 440 445

Ala Tyr Thr Arg His Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe

450 455 460

Gln Gly Phe Ala Leu Val Asn Pro Gln Arg Asn Ser Arg Leu Thr Gly

465 470 475 480

Glu Phe Thr Val Glu Pro Val Pro Glu Gly Ala Gln Leu Ser Phe Gly

485 490 495

Asn Phe Ala Gln Leu Gly His Glu Ser Phe Tyr Trp

500

505

<210> 4

<211> 199

<212> PRT

<213> Homo sapiens

<400> 4

Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala

1

5

10

15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp

20

25

30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro

35

40

45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp

50

55

60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu

65

70

75

80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

85

90

95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe

100

105

110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp

115

120

125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr

130

135

140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
 145 150 155 160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys  
 165 170 175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
 180 185 190

Arg Ser Glu Arg Asn Leu Leu  
 195

<210> 5

<211> 199

<212> PRT

<213> Homo sapiens

<400> 5

Met Lys Trp Val Trp Ala Leu Leu Leu Ala Ala Trp Ala Ala Ala  
 1 5 10 15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp  
 20 25 30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
 35 40 45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
 50 55 60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
 65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

85

90

95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe

100

105

110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp

115

120

125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr

130

135

140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu

145

150

155

160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys

165

170

175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly

180

185

190

Arg Ser Glu Arg Asn Leu Leu

195

<210> 6

<211> 199

<212> PRT

<213> Homo sapiens

<400> 6

Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala

1

5

10

15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp

20

25

30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro  
35 40 45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp  
50 55 60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu  
65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr  
85 90 95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe  
100 105 110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp  
115 120 125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr  
130 135 140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu  
145 150 155 160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys  
165 170 175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly  
180 185 190

Arg Ser Glu Arg Asn Leu Leu  
195

<210> 7

<211> 182



&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 7

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp

1 5 10 15

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro

20 25 30

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp

35 40 45

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu

50 55 60

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

65 70 75 80

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe

85 90 95

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp

100 105 110

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr

115 120 125

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu

130 135 140

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys

145 150 155 160

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly

165 170 175

Arg Ser Glu Arg Asn Leu

180

<210> 8

<211> 193

<212> PRT

<213> Homo sapiens

<400> 8

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
 145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
 165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190

Ile

<210> 9

<211> 193

<212> PRT

<213> Homo sapiens

<400> 9

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
 1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
 20 25 30

Ser Phe Ser Trp Asp Asn Cys Phe Glu Gly Lys Asp Pro Ala Val Ile  
 35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
 50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
 65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85

90

95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100

105

110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115

120

125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130

135

140

Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro

145

150

155

160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165

170

175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180

185

190

Ile

&lt;210&gt; 10

&lt;211&gt; 178

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

Leu Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu

1

5

10

15

Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val

20

25

30

Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn

35 40 45

Val Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro

50 55 60

Leu Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile

65 70 75 80

Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe

85 90 95

Cys Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu

100 105 110

Pro Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly

115 120 125

Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu

130 135 140

Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser

145 150 155 160

Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys

165 170 175

Gly Ile

<210> 11

<211> 200

<212> PRT

<213> Homo sapiens

&lt;400&gt; 11

Arg Ala Gly Pro Pro Phe Pro Met Gln Ser Leu Met Gln Ala Pro Leu

1 5 10 15

Leu Ile Ala Leu Gly Leu Leu Leu Ala Ala Pro Ala Gln Ala His Leu

20 25 30

Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu

35 40 45

Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro

50 55 60

Ile Ile Val Pro Gly Asn Val Thr Leu Ser Val Met Gly Ser Thr Ser

65 70 75 80

Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu Val Leu Glu Lys Glu

85 90 95

Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser

100 105 110

Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp Met Leu Ile Pro Thr

115 120 125

Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr Gly Leu Pro Cys His

130 135 140

Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val

145 150 155 160

Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg

165 170 175

Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys

180 185 190

Ile Ala Ala Ser Leu Lys Gly Ile

195

200

<210> 12

<211> 189

<212> PRT

<213> Homo sapiens

<400> 12

Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu Leu Ala Thr Pro

1

5

10

15

Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp

20

25

30

Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr

35

40

45

Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val Thr Leu Ser Val

50

55

60

Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu

65

70

75

80

Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr

85

90

95

Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp

100

105

110

Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr

115

120

125

Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Pro

130

135

140

Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr  
145 150 155 160

Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg  
165 170 175

Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly Ile  
180 185

<210> 13

<211> 193

<212> PRT

<213> Homo sapiens

<400> 13

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys



100 105 110  
 Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
 115 120 125  
 Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
 130 135 140  
 Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
 145 150 155 160  
 Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
 165 170 175  
 Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190  
 Ile

<210> 14  
 <211> 193  
 <212> PRT  
 <213> Homo sapiens

<400> 14  
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
 1 5 10 15  
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
 20 25 30  
 Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
 35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50

55

60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65

70

75

80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85

90

95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100

105

110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115

120

125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130

135

140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145

150

155

160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165

170

175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180

185

190

Ile

<210> 15

<211> 193

<212> PRT

<213> Homo sapiens

&lt;400&gt; 15

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180 185 190

Ile

&lt;210&gt; 16

&lt;211&gt; 193

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu  
 1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser  
 20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile  
 35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val  
 50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu  
 65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys  
 85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys  
 100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro  
 115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr  
 130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro  
 145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser  
 165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly  
 180 185 190

Ile

<210> 17

<211> 114

<212> PRT

<213> Homo sapiens

<400> 17

Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile  
 1 5 10 15

Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu  
 20 25 30

Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe  
 35 40 45

Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu  
 50 55 60

Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe Ile  
 65 70 75 80

Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His Glu

85

90

95

Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu Gly

100

105

110

Thr Pro

&lt;210&gt; 18

&lt;211&gt; 93

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 18

Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr

1

5

10

15

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp

20

25

30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys

35

40

45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly

50

55

60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val

65

70

75

80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu

85

90

&lt;210&gt; 19

<211> 92

<212> PRT

<213> Homo sapiens

<400> 19

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His

1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu

20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile

35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn

50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile

65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85 90

<210> 20

<211> 92

<212> PRT

<213> Homo sapiens

<400> 20

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His

1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu

20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile

35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn

50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile

65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85 90

<210> 21

<211> 91

<212> PRT

<213> Homo sapiens

<400> 21

Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His Gln

1 5 10 15

Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu Leu

20 25 30

Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile Lys

35 40 45

Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn Gln

50 55 60

Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile Ala

65 70 75 80

Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85 90



<210> 22

<211> 93

<212> PRT

<213> Homo sapiens

<400> 22

Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr

1 5 10 15

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp

20 25 30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys

35 40 45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly

50 55 60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val

65 70 75 80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu

85 90

<210> 23

<211> 92

<212> PRT

<213> Homo sapiens

<400> 23

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His

1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu

20

25

30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile

35

40

45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn

50

55

60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile

65

70

75

80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85

90

<210> 24

<211> 85

<212> PRT

<213> Homo sapiens

<400> 24

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile

1

5

10

15

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu

20

25

30

His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile

35

40

45

Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met

50

55

60

Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly

65

70

75

80

Phe Cys Asp Glu Val

85

&lt;210&gt; 25

&lt;211&gt; 381

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 25

Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Pro Thr

1

5

10

15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys

20

25

30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln

35

40

45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly

50

55

60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn

65

70

75

80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu

85

90

95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys

100

105

110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln

115

120

125

Asn Gln Ile Asp Ser Asn Gly Ile Cys Met His Leu Gly Leu Cys Lys

130 135 140

Ser Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu

145 150 155 160

Pro Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu

165 170 175

Val Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His

180 185 190

Thr Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys

195 200 205

Trp Leu Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys

210 215 220

Gly Ala Leu Arg Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu

225 230 235 240

Val Ala Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile

245 250 255

Leu Leu Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg

260 265 270

Leu Val Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro

275 280 285

Thr Gly Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser

290 295 300

Val Thr Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala

305 310 315 320

Met Leu Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys

325                      330                      335  
 Gln Phe Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg  
                     340                      345                      350  
 Gly Trp Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr  
                     355                      360                      365  
 Met Ser Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu  
                     370                      375                      380

<210> 26  
 <211> 379  
 <212> PRT  
 <213> Homo sapiens

<400> 26  
 Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr  
                     1                      5                      10                      15  
 Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys  
                     20                      25                      30  
 Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln  
                     35                      40                      45  
 Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly  
                     50                      55                      60  
 Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn  
                     65                      70                      75                      80  
 Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu  
                     85                      90                      95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys

100

105

110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln

115

120

125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Leu Gly Cys Lys Ser

130

135

140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro

145

150

155

160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val

165

170

175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr

180

185

190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp

195

200

205

Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly Ala

210

215

220

Leu Arg Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu Val Ala

225

230

235

240

Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu

245

250

255

Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu Val

260

265

270

Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly

275

280

285

Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val Thr

290                      295                      300  
 Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met Leu  
 305                      310                      315                      320  
 Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe  
                     325                      330                      335  
 Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly Trp  
                     340                      345                      350  
 Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met Ser  
                     355                      360                      365  
 Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu  
                     370                      375

<210> 27

<211> 527

<212> PRT

<213> Homo sapiens

<400> 27

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala  
 1                      5                      10                      15  
 Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp  
                     20                      25                      30  
 Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys  
                     35                      40                      45  
 Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp  
                     50                      55                      60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn

65 70 75 80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp

85 90 95

Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser

100 105 110

Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro

115 120 125

Gly Glu Val Cys Ser Ala Leu Asn Leu Cys Glu Ser Leu Gln Lys His

130 135 140

Leu Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro

145 150 155 160

Glu Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro

165 170 175

Leu Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys

180 185 190

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile

195 200 205

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu

210 215 220

His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile

225 230 235 240

Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met

245 250 255

Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly



260	265	270	
Phe Cys Asp Glu Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala			
275	280	285	
Lys Val Ala Ser Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro			
290	295	300	
Ile Lys Lys His Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val			
305	310	315	320
Cys Glu Phe Leu Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys			
325	330	335	
Thr Glu Lys Glu Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu			
340	345	350	
Pro Lys Ser Leu Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly			
355	360	365	
Ser Ser Ile Leu Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val			
370	375	380	
Cys Ser Met Leu His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr			
385	390	395	400
Val His Val Thr Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys			
405	410	415	
Lys Leu Val Gly Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys			
420	425	430	
Gln Glu Ile Leu Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp			
435	440	445	
Pro Tyr Gln Lys Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val			
450	455	460	

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Leu Ile Glu Ile Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu

465                      470                      475                      480

Lys Ile Gly Ala Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu

**485**

Lys Cys Ile Trp Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala

**500**

Ala Gln Cys Asn Ala Val Glu His Cys Lys Arg His Val Trp Asn

**515**

<210> 28

<211> 523

<212> PRT

<213> Homo sapiens

<400> 28

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala

1                      5                      10                      15

Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp

20                      25                      30

Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys

35                      40                      45

Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp

50                      55                      60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn

65                      70                      75                      80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp

85	90	95	
Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser			
100	105	110	
Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro			
115	120	125	
Gly Glu Val Cys Ser Ala Leu Leu Cys Glu Ser Leu Gln Lys His Leu			
130	135	140	
Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro Glu			
145	150	155	160
Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro Leu			
165	170	175	
Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys Asp			
180	185	190	
Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln			
195	200	205	
Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His			
210	215	220	
Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys			
225	230	235	240
Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met			
245	250	255	
His Met Gln Pro Lys Glu Ile Cys Ala Leu Val Gly Phe Cys Asp Glu			
260	265	270	
Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala Lys Val Ala Ser			
275	280	285	

Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro Ile Lys Lys His

290

295

300

Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val Cys Glu Phe Leu

305

310

315

320

Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys Thr Glu Lys Glu

325

330

335

Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu Pro Lys Ser Leu

340

345

350

Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly Ser Ser Ile Leu

355

360

365

Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val Cys Ser Met Leu

370

375

380

His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr Val His Val Thr

385

390

395

400

Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys Lys Leu Val Gly

405

410

415

Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys Gln Glu Ile Leu

420

425

430

Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp Pro Tyr Gln Lys

435

440

445

Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val Leu Ile Glu Ile

450

455

460

Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu Lys Ile Gly Ala

465

470

475

480

Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu Lys Cys Ile Trp  
 485 490 495

Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala Ala Gln Cys Asn  
 500 505 510

Ala Val Glu His Cys Lys Arg His Val Trp Asn  
 515 520

<210> 29

<211> 380

<212> PRT

<213> Homo sapiens

<400> 29

Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Pro Thr  
 1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys  
 20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln  
 35 40 45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly  
 50 55 60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn  
 65 70 75 80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu  
 85 90 95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys  
 100 105 110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln

115

120

125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Gly Leu Cys Lys Ser

130

135

140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro

145

150

155

160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val

165

170

175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr

180

185

190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp

195

200

205

Leu Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly

210

215

220

Ala Leu Ala Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu Val

225

230

235

240

Ala Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu

245

250

255

Leu Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu

260

265

270

Val Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr

275

280

285

Gly Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val

290

295

300

Thr Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met  
 305 310 315 320

Leu Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln  
 325 330 335

Phe Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly  
 340 345 350

Trp Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met  
 355 360 365

Ser Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu  
 370 375 380

<210> 30

<211> 4124

<212> DNA

<213> Homo sapiens

<400> 30

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<210> 31

<211> 579

<212> DNA

<213> Homo sapiens

<400> 31

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 garggnaarg ayccngcngt nathmgnwsn ytnacnytn arcngaycc nathgtngtn 180  
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 gaytayathg gnwsntgyac nttygaray tytgygayg tnytngayat gytnathccn 360  
 acngngarc cntgyccnga rccnytnmgn acntayggny tnccntgyca ytyccntty 420  
 aargarggna cntaywsnyt nccnaarwsn garttygtn tnccngayyt ngarytnccn 480  
 wsntggytna cnacnggnaa ytaymgnath garwsngtny tnwsnwsnws nggnaarmgn 540  
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<210> 32

<211> 633

<212> DNA

<213> Homo sapiens

<400> 32

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 atcgccctgg gcttgcttct cgcgaccctc gcgcaagccc acctgaaaaa ggtgagtgca 180  
 ccccttttta agagtctgtt tgcagcctcc tggcccagct acgggtgtgc gggctcggct 240  
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 ctgttaaccc tgcaccttac tctgacccc cactccttat gtcccccattg ataaggcctg 540  
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<210> 33

<211> 1047

<212> DNA

<213> Homo sapiens

<400> 33

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<210> 34

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 34

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 aagtgagccc catctctaca aaaaatacaa aattagctgg gtgtggtggc atgtgcctgt 240  
 ctgtgtttcc cacctacatg ggaggctgag gcaggaggat cgtctgagcc caggagttg 300  
 aggctgcagt gagtgcagt agccatgata caaaaaaaaa aaataaagaa ttctaagtct 360  
 atgtatagtt cagtgtaggg ggaaaattca catttgatta ttaatgtctg ccatgggcac 420  
 aataatacac tatactaca catgggccac aatgttgcca ttctagaac agactatctc 480  
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 gaagagctgg tatgttgcc ctggaattta cactataac cttttcaa cctttgttt 600  
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<210> 35

<211> 633

<212> DNA

<213> Homo sapiens

<400> 35

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 cctctttta agagtctgtt tgcagcctcc tggcccagct acgggtgtgc gggctctggct 240  
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 agtaactaat tatgggattc tggctgtac aatgaggggt gcctctaaag actgttctg 360  
 ctccaggccc ttttggaaga gattaatctc acgtctgcac tctctgccc tccctcaaag 420  
 cgccggagtg aaaatgcaga cagccttaaa actaaggcat tgccccaag agattcagtc 480  
 ctgtaaccc tgcaccttac tctgacccc cactccttat gtcccatg ataaggcctg 540  
 ctgcctcatc tcttcccctg ctgcaatgcc ctgaggtct cctgagagtt gggagggtt 600  
 gagagcttc caaggccaag aggattcact aag 633

<210> 36

<211> 1047

<212> DNA

<213> Homo sapiens

<400> 36

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 ttccaggctc atcatatcct gccttatagt ttacaatata ctttgggag attatgtct 180

ttgagtcttt tagtttagtc ctgcctataa aatgagtagg ataagtgtta tcccagggtc 240  
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<210> 37

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 37

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 tggaaagtga aggtgaaagg attgcttgag gccaggagtt ccagaccagc ttgggcaaca 180  
 aagtgagccc catctctaca aaaaatacaa aattagctgg gtgtggtggc atgtgcctgt 240  
 ctgtgttcc cacctacatg ggaggctgag gcaggaggat cgtctgagcc caggagttt 300  
 aggtgcagt gagtgcaagt agccatgata caaaaaaaaa aaataaagaa ttctaagtct 360  
 atgtatagtt cagtgtaggg ggaattca catttgatta ttaatgtct ccatgggcac 420  
 aataatacac tatactaca catgggccac aatgttgcca ttctagaac agactatctc 480  
 taagatctca tccagttaa aattctatga ttaaataata ttgctgctt ttgaagaca 540  
 gaagagctgg tatgttgcc ctggaattta cactataac cttttcaaa ctttgttt 600  
 attttttt accagggtga tttagtttg gagaaggagg tggtggcct ctggatcaag 660  
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gagatgggt ttggagagaa gggctttgc atttccttc tgcagatctg catgtctctg 900  
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 ctgggcaag cagccctgac ctaaggga atgagttga cagttctga tagccaggg 1560  
 catctgtgg gctgaccag ttactcatcc ccgttaacat tctctctaaa gagcctcgtt 1620  
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<210> 38

<211> 1043

<212> DNA

<213> Homo sapiens

<400> 38

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 atgcacctgg gctgtctct cgcgacctc gcgcaagccc acctgaaaaa gccatcccag 180  
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 ttccaaagca gtaaggaat gggaacagag tgtttagga cctgaagaat cttatgact 1020  
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<210> 39

<211> 1047

<212> DNA

<213> Homo sapiens

<400> 39

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<210> 40

<211> 1705

<212> DNA

<213> Homo sapiens

<400> 40

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 aagatctcat ccagttaaaa attctatgat taaaatata tctgtctttt tgaagacag 540  
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<210> 41

<211> 1043

<212> DNA

<213> Homo sapiens



<400> 41

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 atgcgcctgg gcttgcttct cgcgaccct ggcgaagccc acctgaaaaa gccatcccag 180  
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 ctgctgggct gaccacgta ctatccccg ttaacattct ctctaaagag cctcgttcat 960  
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<210> 42

<211> 342

<212> DNA

<213> Homo sapiens

<400> 42

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 gtnmgnaarg ayytncaraa yttytnaar aargaraaya araaygaraa rgnathgar 180  
 cayathatgg argayytna yacnaaycn gayaarcary tnwsnttyga rgarttyath 240  
 atgytnatgg cnmgnytnac ntggcnwsn caygaraara tgaygargg ngaygarggn 300  
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<210> 43

<211> 4195

<212> DNA

<213> Homo sapiens

<400> 43

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 gtaattctgt gtttattat ttgaggaaca aactgccgt ttccataac agctgcacta 180  
 ttttacattc ccactaacag tgcattaggc ttccaattct ctatgccctc accaacactt 240  
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<211> 565

<212> DNA

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<211> 430

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<211> 4439

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<213> Homo sapiens

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<213> Homo sapiens

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 aayaaytggg aygtntgygc ngayatggtg ggnacnttya cngayacnga rgayccngcn 300  
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<212> DNA

<213> Homo sapiens

<400> 71

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<210> 72

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<212> PRT

<213> Homo sapiens

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Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro  
 1 5 10 15

<210> 73

<211> 193

<212> PRT

<213> Homo sapiens

<400> 73



Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180 185 190

Ile

<210> 74

<211> 83

<212> PRT

<213> Homo sapiens

<400> 74

Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln Thr

1 5 10 15

Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His Val

20 25 30

Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys Lys

35 40 45

Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met His

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Asp Glu Val

<210> 75

<211> 115

<212> PRT

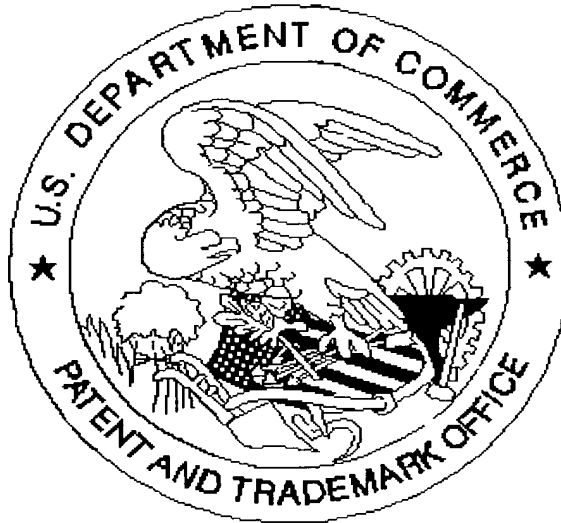
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Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile

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35	40	45	
Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu			
50	55	60	
Asp Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe			
65	70	75	80
Ile Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His			
85	90	95	
Glu Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu			
100	105	110	
Gly Thr Pro			
115			

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for scanning. (Document title)

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*Parts of drawings are dark.*